



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 3

A. R. Katritzky

Advances in
Heterocyclic
Chemistry

Volume 3

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Advances in
HETEROCYCLIC
CHEMISTRY

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Preface

The third volume of this series covers three specific groups of compounds: the carbolines (reviewed by R. A. Abramovitch and I. D. Spenser), the thiatriazoles (K. A. Jensen and C. Pedersen), and the pentazoles (I. Ugi). The remaining four chapters deal with topics of general chemical interest from the heterocyclic viewpoint: the quaternization of heterocyclics (G. F. Duffin), carbene reactions (C. W. Rees and C. E. Smithen), applications of the Hammett equation (H. H. Jaffé and H. Lloyd Jones), and some aspects of the nucleophilic substitution of heterocyclic azines (G. Illuminati).

Suggestions for contributions to subsequent volumes of the series are welcomed; they should be submitted in the form of a short synopsis.

Thanks are due to the authors for their cooperation, the members of the Editorial Board, and the publishers. I am especially grateful to the assistant editors, Dr. A. J. Boulton and Dr. J. M. Lagowski, for all their help.

A. R. KATRITZKY

Norwich, England
April, 1964

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A. R. KATRITZKY AND J. M. LAGOWSKI

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E. BULKA

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N. K. KOCHETKOV AND S. D. SOKOLOV

ERRATA

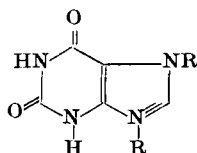
In Volume 1, in the chapter on Prototropic Tautomerism by A. R. Katritzky and J. M. Lagowski,
p. 326, the equation should read

$$K_T = \frac{K_1}{K_{(\text{HXMe}^+)}} - 1 = \frac{K_{(\text{MeXH}^+)}}{K_1 - K_{(\text{MeXH}^+)}}$$

In Volume 2, in the chapter on Prototropic Tautomerism by A. R. Katritzky and J. M. Lagowski,

p. 7, line 9, vitamin A (**34**) should read vitamin C (**34**); index entry on p. 458, Vitamin A, tautomerism, 7 should read Vitamin C, tautomerism, 7

p. 59, formula [138] should be



In Volume 2, in the chapter on Free-Radical Substitutions of Heteroaromatic Compounds by R. O. C. Norman and G. K. Radda,

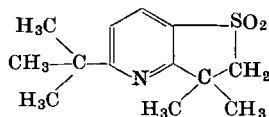
p. 156, Table VI, 5-R-Acridine should read 9-R-Acridine

p. 157, lines 17 and 18, 5-phenylacridine should read 9-phenylacridine

p. 157, lines 19 and 20, 5,10-dibenzylacridan should read 9,10-dibenzylacridan

p. 157, line 26 and p. 158, line 1, 5-phenylacridine should read 9-phenylacridine

p. 175, formula (**43**) should be



p. 176, line 30, pheny radical should read phenyl radical

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The Quaternization of Heterocyclic Compounds

G. F. DUFFIN

Minnesota 3M Research Ltd.

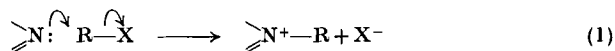
Pinnacles, Harlow, Essex, England

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I. Introduction

If a nitrogen atom in a heterocyclic ring possesses a pair of electrons not already involved in the formation of σ or π bonding orbitals, those electrons may form a bond between that nitrogen atom and a carbon atom of suitable polarizability, the nitrogen atom becoming quaternary. The attacking molecule must be one which can split off an anion during the quaternization and alkyl halides are therefore the most usual reagents. This reaction of heterocyclic compounds is therefore one type of Menshutkin reaction.

This reaction may be regarded in two ways. The first is to see the reaction as a nucleophilic replacement of the halogen or similar group by attack of the electron pair of the base as in Eq. (1),



and, as will be seen, the reaction is bimolecular. This view shows the parallel between quaternary salt formation and the hydrolysis of an alkyl halide. Alternatively, the quaternization process may be regarded as a special type of electrophilic attack on the ring which normally takes place only at a nitrogen atom, although in certain cases reaction at carbon may also occur. It will be seen that a consideration of the reaction in this second sense helps in the correlation of the effect of substituents on the quaternization process with those of substituents on the reactivity of substituted benzenes.

It would therefore be deduced that the availability of the electron pair, as influenced by the ring containing the nitrogen atom, the substituents present in that ring, and the steric environment, should affect the rate of quaternization. Furthermore, the solvent for the reactants and the nature of the group R in Eq. (1) would be expected to be important factors in determining the course of the reaction. In the following sections the importance of each of these factors is considered.

In addition to direct attack on the nitrogen atom which finally becomes the quaternary center, it is possible for the electrophile to attack elsewhere in the heterocyclic molecule and for a mesomeric shift to proceed to completion to give a salt.

II. Reagents for Quaternization

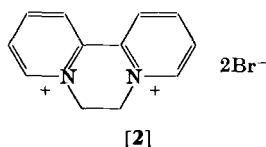
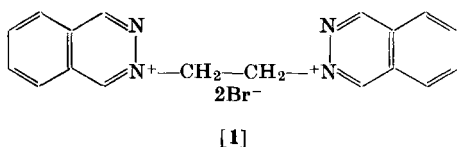
A. ALKYL HALIDES AND RELATED COMPOUNDS

By far the commonest reagents for the formation of heterocyclic quaternary salts are the alkyl halides, and, indeed, methiodides out-

number all the other salts reported. The order of reactivity of the alkyl derivatives is $I > Br \gg Cl$ ¹; no alkyl fluorides have been reported to take part in the reaction.

Primary halides are more reactive than secondary compounds²⁻⁴; quaternary salt formation does not occur with tertiary halides, elimination always occurring to give the hydriodide and an olefin.⁵ Also, the larger the alkyl group the slower is the reaction⁶; this is shown by the very slow reaction of dodecyl bromide with quinoline,⁷ and even butyl iodide is much slower to react than methyl iodide.^{8, 9} The longer chain primary halides commonly undergo elimination rather than cause quaternization; for example, *n*-octyl and cetyl iodides give only the hydriodides when heated with 9-aminoacridine.¹⁰

There has been much interest recently in the reaction of α , ω -dihalogenoalkanes. 1,2-Dibromoethane reacts with phthalazine to give ethane 1,2-bis-phthalazinium dibromide (1),¹¹ none of the mono salt being formed directly, but the same dibromo compound¹² and α , α' -dipyridyl give the cyclic compound 2.¹²



¹ R. P. Larsen and C. A. Kraus, *Proc. Natl. Acad. Sci. U.S.* **40**, 70 (1954); *Chem. Abstr.* **48**, 7996 (1954).

² H. C. Brown and A. Cahn, *J. Am. Chem. Soc.* **77**, 1715 (1955).

³ C. A. Bunton, C. H. Greenstreet, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.* 647 (1954).

⁴ W. Cuisa and L. Lipparini, *Gazz. Chim. Ital.* **90**, 147 (1960); *Chem. Abstr.* **52**, 2850 (1958).

⁵ H. C. Brown and N. Nakagawa, *J. Am. Chem. Soc.* **78**, 2197 (1956).

⁶ S. K. Mukherjee and S. R. Palit, *J. Indian Chem. Soc.* **27**, 175 (1950); *Chem. Abstr.* **45**, 425 (1951).

⁷ A. V. Few, A. R. Gilby, R. H. Ottewill, and H. C. Parriera, *J. Chem. Soc.* 1489 (1958).

⁸ J. Druey and H. U. Daeniker, U.S. Patent 2,945,037 (1956).

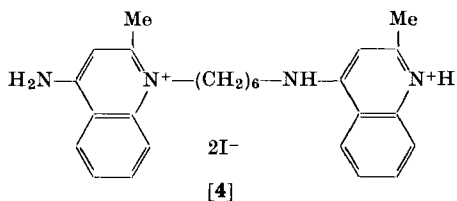
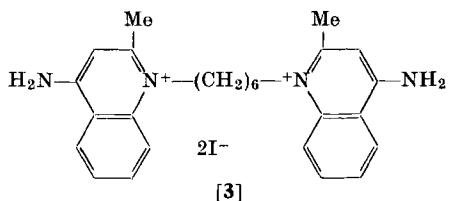
⁹ R. M. Fuoss, M. Watanabe, and B. D. Coleman, *Mezhdunar. Simpozium po Makromolekul. Khim., Dok., Moscow* **3**, 134 (1960); *Chem. Abstr.* **55**, 7411 (1961).

¹⁰ I. S. Joffe and N. A. Selezneva, *Zh. Obschch. Khim.* **31**, 50 (1961); *Chem. Abstr.* **55**, 24751 (1961).

¹¹ J. Druey and H. U. Daeniker, U.S. Patent 2,945,036 (1956).

¹² R. F. Homer and T. E. Tomlinson, *J. Chem. Soc.* 2498 (1960).

A range of bis-quaternary salts from various bases and α - ω compounds is described by Libman *et al.*,¹³ while the reactions of 4-aminoquinoline and similar dihalogen compounds have been studied by Austin *et al.*¹⁴ These workers discovered that the crude product obtained from the reaction of dihexamethylene diiodide with 4-aminoquinoline was very active against *Trypanosoma congolense* whereas the purified product was very low in activity. The main product was the expected 1,1'-bis salt **3**, and the active impurity (about 10% of the total yield) was the unsymmetrical derivative **4**.



In spite of the fact that the vast majority of quaternizations of amino-heterocyclic compounds are reported as occurring on the ring nitrogen atom only, it seems quite likely that salt formation may also take place on the exocyclic nitrogen in other cases but that it has been overlooked in the absence of a test such as was available for **4**.

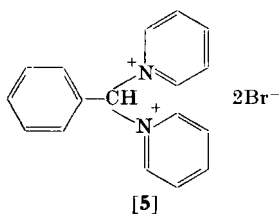
The formation of quaternary salts from benzyl halides and related compounds occurs readily and has been known for many years. More recently, Kröhnke and co-workers, who have studied the reactions of many heterocyclic quaternary salts, reported the formation of **5** from pyridine and benzylidene dibromide on heating the reactants together for 1 hr at 100°. ¹⁵ The salt is sufficiently stable to be recrystallized from methanol containing a trace of hydrogen bromide. Isoquinoline gives a similar salt.

¹³ D. D. Libman, D. L. Pain, and R. Slack, *J. Chem. Soc.* 2305 (1952).

¹⁴ W. C. Austin, M. D. Potter, and E. P. Taylor, *J. Chem. Soc.* 1489 (1958).

¹⁵ F. Kröhnke and H. Leister, *Chem. Ber.* **91**, 1295 (1958).

Pyridine and chloroacetic acid react normally to give the stable betaine derivative, but 2,5-dimethylpyrazine is quite different in its behavior. Chloroacetic acid is without action while both bromo- and iodo-acetic acid react smoothly, more rapidly in nitrobenzene than in



benzene, to give 1,2,5-trimethylpyrazinium salts with the loss of carbon dioxide.¹⁶ It has been suggested that the decarboxylation is facilitated by the participation of the second nitrogen atom. Quinoxaline and bromoacetic acid yielded a small amount of carbon dioxide, but no quaternary salt could be isolated from the reaction mixture.

The reaction between phenacyl bromide and pyridine to give salts of type **6** (R = Ph) was first described by Kröhnke,¹⁷ and more recently there has been widespread interest in this type of salt.¹⁸⁻²⁰ The phenacyl halide, or similar halogen compound, may be prepared *in situ* by the reaction of iodine or bromine with the appropriate methyl ketone, and this method has been applied to the preparation of pyridinium salts, in particular where R is a phenyl,²⁰ *p*-fluorophenyl,²¹ 2-, 3- or 4-pyridyl,²² 3-indolyl,²³ or 2-thienyl group.²⁴ This method is not always satisfactory and fails with acetophenone, iodine, and quinoline, while the corresponding salt from 4-picoline is difficult to purify; in these two cases it is only Kröhnke's original method which gives good yields.²⁰ The hetero ring in this class of compounds has been pyridine or a substituted pyridine,¹⁹ quinoline,

¹⁶ E. V. Hart and P. E. Spoerri, *J. Am. Chem. Soc.* **77**, 5898 (1955).

¹⁷ F. Kröhnke, *Ber.* **68**, 1177 (1935).

¹⁸ L. C. King, *J. Am. Chem. Soc.* **66**, 894 (1944).

¹⁹ L. C. King and M. McWhirter, *J. Am. Chem. Soc.* **68**, 717 (1946).

²⁰ J. L. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.* **68**, 868, 1131 (1946).

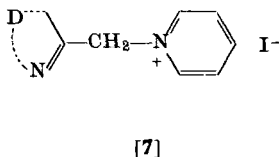
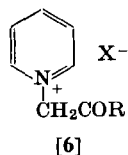
²¹ C. T. Bahner, W. T. Easley, B. G. Walden, H. D. Lyons, and G. E. Biggerstaff, *J. Am. Chem. Soc.* **74**, 3960 (1952).

²² F. Kröhnke and K. F. Gross, *Chem. Ber.* **92**, 22 (1959).

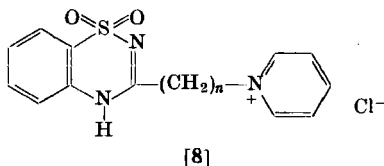
²³ G. Hart and K. T. Potts, *J. Org. Chem.* **27**, 2940 (1962).

²⁴ L. C. King, M. McWhirter, and R. L. Rowland, *J. Am. Chem. Soc.* **70**, 240 (1948).

isoquinoline,^{19,20} pyrazine,²¹ and quinoxaline.²⁵ The halogenoacetones behave similarly to give salts (cf. 6; R = Me), although in the case of the sterically hindered 2-phenylpyridine only iodoacetone gives a quaternary salt.²⁶



In a similar manner to a methyl ketone, heterocyclic compounds with a reactive methyl group may be condensed with iodine and pyridine to give a quaternary salt of type 7; for example, 2-methylbenzothiazole gives a high yield of the salt after 6 hr at 100°. Reid and Bender found that D in such salts (cf. 7) could also be derived from 2-methylquinazoline, 2-methylbenzoxazole, and 2-methylbenzothiazole.²⁷ The reactive methyl compound may also be 2-picoline N-oxide, though the latter compound is surprisingly slow to react.²⁸



3-Chloromethylbenzo-1,2,4-thiadiazine 1,1-dioxide forms quaternary salts, e.g. 8 ($n = 1$), with pyridine, 2- and 3-picolines, and isoquinoline, but the 3-(2'-chloroethyl) compound gives a lower yield of the salt, e.g. 8 ($n = 2$), because some of the halogen derivative is converted into the 3-vinyl compound.²⁹

Pearson *et al.*³⁰ have presented a useful compilation of the reactivity

²⁵ W. T. Easley and C. T. Bahner, *J. Chem. Soc.* 710 (1942).

²⁶ C. K. Bradsher and L. F. Beavers, *J. Am. Chem. Soc.* **77**, 453 (1955).

²⁷ W. Reid and H. Bender, *Chem. Ber.* **89**, 1893 (1956).

²⁸ M. Hamana, B. Umezama, Y. Goto, and K. Noda, *Chem. Pharm. Bull. (Tokyo)* **8**, 692 (1960); *Chem. Abstr.* **55**, 18723 (1961).

²⁹ L. Raffa, R. Cameroni, and M. T. Bernabei, *Farmaco (Pavia), Ed. Sci.* **15**, 842 (1960); *Chem. Abstr.* **55**, 19944 (1961).

³⁰ R. G. Pearson, S. H. Sanger, F. V. Williams, and W. J. MacGuire, *J. Am. Chem. Soc.* **74**, 5130 (1952).

of a number of alkyl bromides with pyridine in methanol. Their results are given in Table I.

TABLE I
SECOND ORDER REACTION RATES FOR PYRIDINE AND
ALKYL BROMIDES IN METHANOL AT 35°³⁰

Alkyl compound	K (l/mole min)
Ethylene bromohydrin	1.7×10^{-5}
2-Phenoxyethyl bromide	2.0×10^{-5}
<i>n</i> -Propyl bromide	1.0×10^{-4}
Ethyl bromide	2.3×10^{-4}
2,4,6-Trimethylphenacyl bromide	2.5×10^{-4}
Alkyl bromide	8.3×10^{-3}
Benzyl bromide	3.1×10^{-2}
Ethyl bromoacetate	8.5×10^{-3}
Phenacyl bromide	4.5×10^{-2}
<i>p</i> -Bromophenacyl bromide	7.2×10^{-2}

B. ARYL AND HETEROCYCLYL HALIDES

Heterocyclic bases which readily form quaternary salts with the more usual reagents will also react with suitably activated aryl and heterocyclyl halogen compounds, the classic case being the salt formed from pyridine and 1-chloro-2,4-dinitrobenzene. Reactions of this type have been studied by Chapman *et al.*^{31, 32} Salt formation between pyridine and 3- and 4-picolines on the one hand, and between 1-chloro-2,4-dinitrobenzene and 2- and 4-chloro-3-nitropyridine and 2-chloro-5-nitropyridine on the other, was investigated. The expected higher activity of the two picolines was attributed to the increase in electron density produced by induction and hyperconjugation, but the overall lower reactivity of the pyridine compounds in comparison to that of aniline derivatives of similar basicity was believed to be due to the interaction of the *o*-nitro group in the transition state, which could assist the latter but not the former. Further suggestions were made later³² and are discussed in Section VI. As would be expected, picryl chloride is a very reactive quaternizing reagent and reacts easily with pyridine, the picolines (including the 2-isomer), quinoline, and iso-

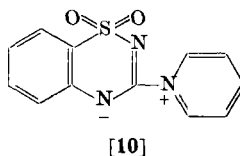
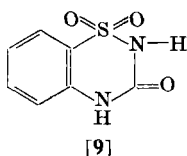
³¹ E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.* 3392 (1953).

³² R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.* 437 (1952).

quinoline,³³ but the formation of a 1:1 adduct between 1-fluoro-2,4-dinitrobenzene and quinoline is less expected and the adduct may not be a true salt.¹⁵

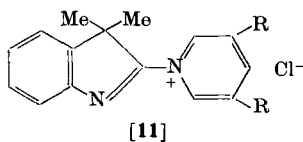
Most N-phenyl quaternary salts are not prepared by direct quaternization but rather by introducing the nitrogen substituent before ring closure. It has recently been found that diphenyl iodonium borofluoride reacts smoothly with pyridine; the phenyl carbonium ions formed give the 1-phenylpyridinium ion good yield.³⁴

Many heterocyclic halogen compounds are capable of quaternizing nitrogen bases and, indeed, of self-condensation, which can occur with great ease (for example, on warming a solution of 1-chloro-4-methyl-



phthalazine resinification occurs). A very useful product of this type is 4-pyridylpyridinium chloride, obtained originally by Koenigs and Greiner,^{34a} the preparation of which from pyridine and thionyl chloride has been improved.³⁵ An interesting quaternization in which a heterocyclic halide would appear to be an intermediate is the reaction between 3,4-dihydro-3-oxobenzo-1,2,4-thiadiazine 1,1-dioxide (9), pyridine, and *m*-nitrobenzenesulfonyl chloride to give the betaine 10.³⁶ The same process in the presence of quinoline or 2,4-lutidine instead of pyridine gave only the *m*-nitrobenzenesulfonate of 9, but isoquinoline behaved like pyridine.

Both pyridine and 3,5-lutidine react with 2-chloro-3,3-dimethyl-



³³ K. Okoń, *Bull. Acad. Polon. Sci., Ser. Sci. Chim. Geol. Geograph.* **6**, 331 (1958); *Chem. Abstr.* **52**, 20153 (1958).

³⁴ A. N. Nesmeyanov, L. G. Makarova, and T. P. Tolstaya, *Tetrahedron* **1**, 145 (1957).

^{34a} E. Koenigs and H. Greiner, *Ber.* **64**, 1052 (1931).

³⁵ K. Bowden and P. N. Green, *J. Chem. Soc.* 1795 (1954).

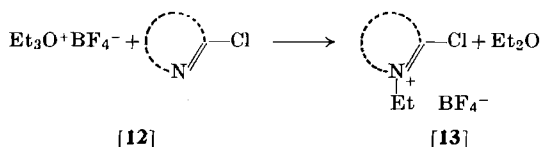
³⁶ L. Raffa, M. Di Bella, M. Melagori, and G. Vanysa, *Farmaco (Pavia), Ed. Sci.* **16**, 3 (1961); *Chem. Abstr.* **55**, 19945 (1961).

indolenine to give quaternary salts (**11**; R = H or Me); these reactions proceed more readily than the corresponding quaternizations involving 2-chloro-benzoxazole and -benzothiazole.³⁷

C. OTHER QUATERNIZING REAGENTS

Although alkyl halides are the commonest reagents used for quaternization, many others have been used and some of the more recently described substances are of interest.

The action of methyl iodide on chloro-substituted heterocyclics usually results, in addition to quaternization, in the replacement of the chlorine by iodine³⁸ if the halogen is in a position *alpha* or *gamma* to the quaternary center, particularly so in the former case.³⁹ This type of replacement is less likely if dimethyl sulfate is used but may still occur to give a sulfate betaine⁴⁰ (see Section IV, C). An easy method to obtain α -halogeno-quaternary salts has recently been discovered by Balli and Kersting⁴¹ who reacted the readily accessible triethyloxonium borofluoride **12**⁴² with a variety of bases. The very



reactive chloro salts (**13**) were obtained from 2-chloro-quinoline, -benzothiazole, -benzoselenazole, -benziminazole and from 5-chloro-3-methyl-1-phenyl-1,2,4-triazole; the last named compound reacted at the 4-position.

Although the uses of dimethyl sulfate and methyl toluene-*p*-sulfonate are well known, in many cases these reagents have been used in solution, e.g. in nitrobenzene,^{43, 44} in addition to the older

³⁷ G. E. Ficken and J. D. Kendall, *J. Chem. Soc.* 3988 (1959).

³⁸ H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.* **16**, 1143 (1951).

³⁹ A. D. Ainley, F. H. S. Curd, W. Hepworth, A. G. Murray, and C. H. Vasey, *J. Chem. Soc.* 59 (1953).

⁴⁰ H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.* 1858 (1953).

⁴¹ H. Balli and F. Kersting, *Ann. Chem.* **647**, 1 (1961).

⁴² H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939).

⁴³ S. S. Berg, *J. Chem. Soc.* 4041 (1961).

⁴⁴ Y. S. Rozum, *Zh. Obshch. Khim.* **30**, 1661 (1960); *Chem. Abstr.* **55**, 1631 (1961).

fusion processes. Some bases which are difficult to quaternize have been found by Kiprianov and co-workers to give *N*-methyl quaternary salts in good yield by fusion with methyl *o*-nitrobenzenesulfonate⁴⁵ or, better, with methyl 2,4-dinitrobenzenesulfonate.⁴⁶

D. SOLVENTS

The importance of the solvent, in many cases an excess of the quaternizing reagent, in the formation of heterocyclic salts was recognized early. The function of dielectric constants and other more detailed influences on quaternization are dealt with in Section VI, but a consideration of the subject from a preparative standpoint is presented here. Methanol and ethanol are used frequently as solvents, and acetone,⁴⁷ chloroform,²⁵ acetonitrile,⁸ nitrobenzene,⁴³ and dimethylformamide⁴⁸ have been used successfully. The last two solvents were among those considered by Coleman and Fuoss in their search for a suitable solvent for kinetic experiments⁴⁹; both solvents gave rise to side reactions when used for the reaction of pyridine with *n*-butyl bromide. Their observation with nitrobenzene is unexpected, and no other workers have reported difficulties. However, tetramethylene sulfone, 2,4-dimethylsulfolane, ethylene and propylene carbonates,⁴⁹ and salicylaldehyde⁵⁰ were satisfactory, giving relatively rapid reactions and clean products. Ethylene dichloride, used quite frequently for Friedel-Crafts reactions, would be expected to be a useful solvent but has only recently been used for quaternization reactions.⁴¹

The problem of the isolation of quaternary salts, even when formed, is, in some cases, an acute one. Water or ethanol is frequently held very tenaciously⁵¹ and this possibility may be the reason that so many workers still use non-hydric solvents, such as benzene,¹⁴ despite the fact that reactions in such solvents are usually slow⁶; clearly the best solvents are the non-hydric ones of high dielectric constant.

⁴⁵ S. G. Fridman and A. I. Kiprianov, *Uk. Khim. Zh.* **22**, 767 (1956); *Chem. Abstr.* **51**, 8725 (1957).

⁴⁶ A. I. Kiprianov and A. I. Tolmachev, *Zh. Obshch. Khim.* **27**, 142 (1957); *Chem. Abstr.* **51**, 12912 (1957).

⁴⁷ V. S. Padmanabhan and S. V. Anantakrishnan, *Proc. Indian Acad. Sci., Sect. A*, **40**, 132 (1945); *Chem. Abstr.* **49**, 2840 (1955).

⁴⁸ F. G. White and L. I. Ingraham, *J. Am. Chem. Soc.* **82**, 4114 (1960).

⁴⁹ B. D. Coleman and R. M. Fuoss, *J. Am. Chem. Soc.* **77**, 5472 (1955).

⁵⁰ T.-C. Li, W.-C. Li, and C.-E. Sun, *Hua Hsueh Hsueh Pao* **22**, 386 (1956); *Chem. Abstr.* **52**, 10698 (1958).

⁵¹ D. J. Fry, J. D. Kendall, and A. J. Morgan, *J. Chem. Soc.* 5062 (1960).

III. The Influence of Substituents in Mono-*N*-Heterocycls

A. AROMATIC COMPOUNDS

In arriving at a picture of the influence of various substituents in aromatic heterocyclic compounds on quaternization, it is very difficult to separate the functions of electronic and steric effects.

The most thoroughly investigated compounds are the alkylpyridines. Coleman and Fuoss compared the reactions of pyridine, 4-picoline, and 4-isopropylpyridine with *n*-butyl bromide and found a steady increase in the rate in the order given; the activation energies are 16.0, 15.95, and 15.6 kcal per mole, respectively.⁴⁹ Brown and Cahn carried out a detailed study of the reactions of 2-, 3-, and 4-alkylpyridines with methyl, ethyl, and isopropyl iodides in nitrobenzene²; the results are given in Table II. These data show the higher activation

TABLE II
ENERGY OF ACTIVATION (KCAL PER MOLE) FOR
THE REACTION OF ALKYL IODIDES WITH
PYRIDINES²

Pyridine substituent	MeI	EtI	<i>iso</i> -PrI
None	13.9	16.0	17.7
2-Me	14.0	16.5	19.2
2-Et	14.2	16.6	—
2-Isopropyl	14.8	17.1	—
2- <i>t</i> -Butyl	17.5	—	—
3-Me	13.6	15.5	17.4
4-Me	13.6	15.8	17.3
4- <i>t</i> -Butyl	13.7	—	—

energy with the 2-substituted compounds and the sharp increase with the bulk of the substituent or the size of the entering alkyl group. A small, but significant, activating influence is seen for a 3- or 4-alkyl group which, however, is very similar for methyl or *t*-butyl groups in the 4-position. Other data from the same study indicate that as the 3-alkyl group increases in size, and presumably therefore in its inductive effect, there is a steady increase in the rate of quaternization in the series 3-methyl < 3-ethyl < 3-isopropyl < 3-*t*-butyl. Brown and Barbaras⁵² have discussed the relative merits of hyperconjugation and inductive effects in the reaction of trimethylborane with pyridine,

⁵² H. C. Brown and G. K. Barbaras, *J. Am. Chem. Soc.* **69**, 1137 (1947).

where steric effects are very pronounced. A comparison of the figures in Table II with the heat of reaction of methanesulfonic acid and alkyl pyridines in nitrobenzene,⁵³ in which case the order is 2- and 4-methylpyridine > pyridine > 3-methylpyridine and the heat of reaction only slowly decreases as the group in the 2-position becomes larger, shows that one is concerned with quite different effects in quaternization and in salt formation and indicates that thermodynamic considerations are operative in protonation but kinetic influences preponderate in quaternization. Clearly the order of proton attack suggests a hyperconjugative or similar effect, whereas in quaternization the steric influence is very strong. A similar activating influence is shown in the reactions of 4-picoline and pyridine with butyl bromide in 2,4-dimethylsulfolane where the picoline reacts at almost twice the rate of pyridine.⁵⁴

Very strong steric effects are also shown with 2-phenylpyridine,^{55, 26} and an examination, by Packer *et al.*,⁵⁶ of the reaction of methyl iodide with isoquinoline, pyridine, quinoline, and 2- and 8-methylquinoline shows an increasing activation energy in that order, the values being 13.54, 13.68, 14.79, 16.02, and 18.80 kcal/mole, respectively; again steric hindrance is the operative factor. An interesting case involving steric hindrance is the failure of 2-methylbenzothiazole to react with isopropyl iodide; benzothiazole itself gives a salt with the same iodide.⁵⁷

The influence of other groups in a pyridine or similar ring system is more difficult to assess because no kinetic data are available. The deactivating effect of the bromine atom in the 2-position is greater than that in the 3-position,²¹ while 2,6-dibromopyridine is very slow to react with dimethyl sulfate.⁵⁸ Esters, amides, and nitriles of nicotinic and isonicotinic acids undergo fairly easy quaternization^{59, 60} at about

⁵³ H. C. Brown and R. R. Holmes, *J. Am. Chem. Soc.* **77**, 1727 (1955).

⁵⁴ E. Hirsch and R. M. Fuoss, *J. Am. Chem. Soc.* **77**, 6115 (1955).

⁵⁵ A. I. Kiprianov and V. A. Shrubovich, *Zh. Obshch. Khim.* **29**, 1290 (1959); *Chem. Abstr.* **54**, 9955 (1960).

⁵⁶ J. Packer, J. Vaughan, and E. Wang, *J. Am. Chem. Soc.* **80**, 905 (1958).

⁵⁷ L. G. S. Brooker, Abstr. of Papers, 117th Meeting, Am. Chem. Soc., Philadelphia, Pa., April 1950, p. 38L.

⁵⁸ J. P. Wibaut, B. W. Speekman, and H. M. von Wagtenonk, *Rec. Trav. Chim.* **58**, 110 (1939).

⁵⁹ G. Pfeleiderer, E. Sann, and A. Stock, *Chem. Ber.* **93**, 3083 (1960).

⁶⁰ E. M. Kosower, D. Hofmann, and K. Wallenfels, *J. Am. Chem. Soc.* **84**, 2756 (1962).

the same rate,⁴ but the joint influence of halogen substituents in the 2- or 6-positions and an amide group in the 3-position prevents reaction between 2- or 6-chloro- and -bromo-nicotinamides and methyl or ethyl iodide in sealed tubes at 100°.⁶¹ The corresponding 2- or 6-halogeno-3-picolines react normally,³⁸ as do the 2-fluoronicotinamides, although replacement of the fluorine by a hydroxyl group also occurs.⁶¹ 2-Chloroquinoline reacts slowly with methyl iodide,³⁸ and, although 8-chloroquinoline quaternizes fairly easily at 100°, 6-acet-amido-8-chloroquinoline requires treatment with methyl toluene-*p*-sulfonate at 200°.⁶²

Pyridine aldoximes may be quaternized with dimethyl sulfate by refluxing in benzene or ethanol for 3 hr,⁶³ but 2-acetyl-4-methyl-thiazole proved very difficult to convert into its methiodide. Breslow and McNelis failed to achieve direct quaternization and obtained the salt only by forming the ketal with ethylene glycol, quaternizing, and subsequently hydrolyzing to the ketone.⁶⁴ Later, Daigo and Reed obtained the salt in low yield by direct reaction with excess methyl iodide at 80° for 64 hr,⁶⁵ while White and Ingraham used prolonged treatment with methyl iodide in dimethyl formamide to quaternize the 2-benzoyl compound.⁴⁸ Apparently an electronic effect rather than a steric influence is operative here.

One type of substituent on pyridine which has been of some interest is that of another nitrogen-containing heterocyclic ring. Homer discovered that 2,4'-dipyridyl gave only a monomethiodide on mild treatment with methyl iodide and that the bismethiodide was formed with an excess of the reagent, while the corresponding 4,4'-dipyridyl gave the bis-salt much more easily.⁶⁶ Duffin *et al.* reported a series of 3- and 4-pyridyl heterocyclic compounds, all of which, although not reacting with the same ease, gave the pyridinium salts.⁶⁷

B. SATURATED RINGS

In a saturated heterocyclic compound the situation is very different from that in an aromatic compound. The volume requirement of a

⁶¹ H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.* **14**, 509 (1949).

⁶² W. O. Sykes, *J. Chem. Soc.* 544 (1953).

⁶³ A. L. Green, U.S. Patent 2,996, 510 (1960).

⁶⁴ R. Breslow and E. McNelis, *J. Am. Chem. Soc.* **81**, 3080 (1959).

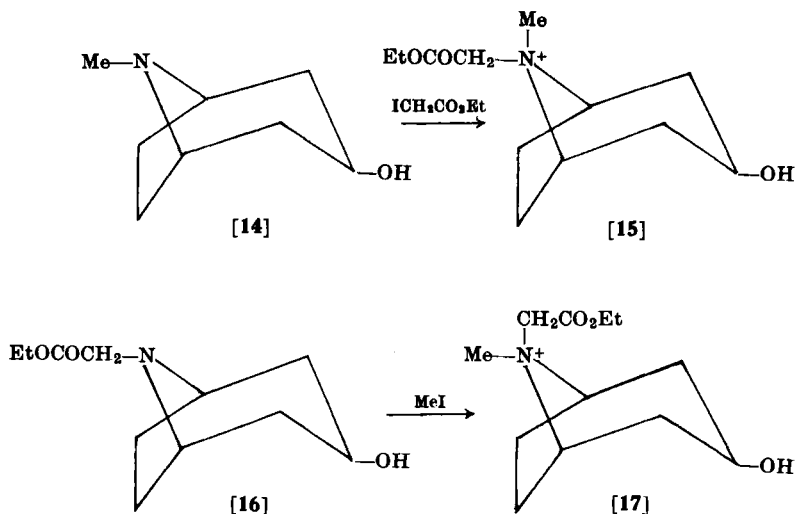
⁶⁵ K. Daigo and L. J. Reed, *J. Am. Chem. Soc.* **84**, 659 (1962).

⁶⁶ R. F. Homer, *J. Chem. Soc.* 1574 (1958).

⁶⁷ G. F. Duffin, D. J. Fry, H. R. J. Waddington, and A. J. Morgan, British Patent 875,887 (1961).

lone pair of electrons has been reputed to be larger than that of a hydrogen atom and may even approach that of a methyl group.⁶⁸ Fodor found that the quaternizing group usually enters at the equatorial position,⁶⁹ but it has been argued that this does not permit one to assign a conformation to the original base which N.M.R. spectral data indicate exists in equilibrium in solution.⁷⁰

The different configurations of the salts obtained by varying the sequence of alkylation are well illustrated by the reaction of pseudotropine (**14**) with ethyl iodoacetate to give **15**, while the opposite order



of reaction gave **17** from **16**.⁷¹ The lack of a direct correlation between the outcome of quaternization and the conformation of the original base was also brought out in a recent communication by Moynehan *et al.* who synthesized the *cis* and *trans* isomers, relative to the 10-hydrogen atom, of 1-, 2-, 3-, and 4-methylquinolizidine.⁷² The quaternization of these bases and of quinolizidine itself showed that two series of salts are obtainable. Salts of the *trans*-configuration

⁶⁸ M. Aroney and R. J. W. Le Fevre, *J. Chem. Soc.* 3002 (1958).

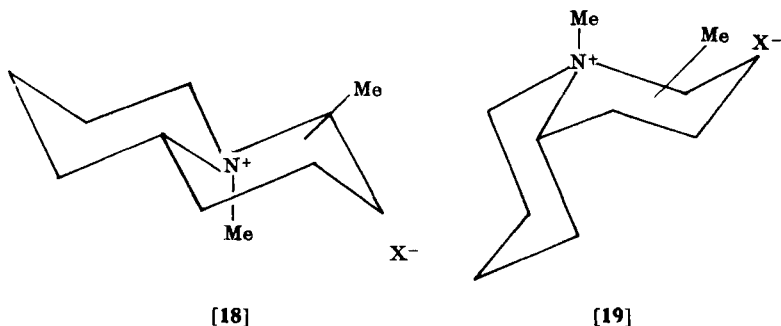
⁶⁹ G. Fodor, *Tetrahedron* **1**, 87 (1957).

⁷⁰ G. L. Closs, *J. Am. Chem. Soc.* **81**, 5456 (1959).

⁷¹ G. Fodor, J. Toth and I. Vincze, *J. Chem. Soc.* 3504 (1955).

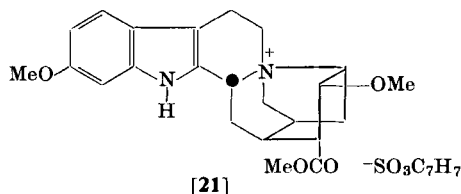
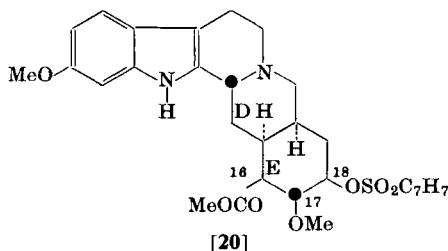
⁷² T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.* 218 (1961); *J. Chem. Soc.* 2367 (1962).

(cf. 18) are obtained when that configuration places the *C*-methyl groups equatorially, but those bases in which approach to the lone pair of electrons on nitrogen in the *trans*-configuration is hindered by axial *C*-methyl groups give *cis*-salts (cf. 19). Direct quaternization of



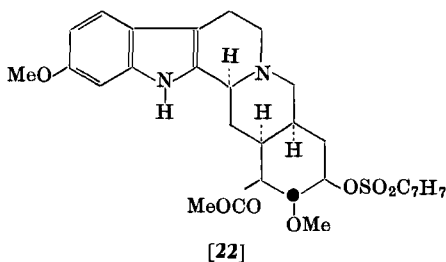
quinolizidine itself gives the salt 18, as do the *trans*-1- and -3-methyl compounds, but *cis*-1- and -3-methyl derivatives give the *cis*-fused salts.

A very interesting internal quaternization was discovered during the final proof of the configuration of reserpine.⁷³ Attempted detos-



⁷³ P. E. Aldrich, P. A. Diassi, D. F. Dickel, C. M. Dylion, P. D. Hance, C. F. Huebner, B. Korzun, M. E. Kuehne, L. H. Liu, H. B. MacPhillamy, E. W. Robb, D. K. Roychaudhuri, E. Schittler, A. F. St. André, E. E. van Tamelen, F. L. Weisenborn, E. Wenkert, and O. Wintersteiner, *J. Am. Chem. Soc.* **81**, 2481 (1959).

ylation of methyl reserpate tosylate (**20**) with 2,4,6-collidine gave a quaternary salt of structure **21**. The fact that a reaction of this type occurs in a solvent with a relatively low dielectric constant suggests that a fully intramolecular change takes place by a concerted mechanism, and in this case the 17-methoxy group also assists by neighboring-group participation. This evidence clearly proves the *cis* relationship of the D and E rings and also explains the failure of the corresponding isoreserpine derivatives, which possess structures such as **22**, to give



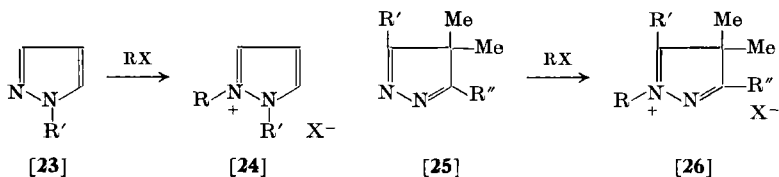
quaternary salts; steric interference between the 16-methoxycarbonyl group and the indole ring prevents a sufficiently close approach of the tertiary nitrogen and the carbon atom carrying the tosyloxy group.

IV. The Position of Quaternization in Monocyclic Compounds

Many of the quaternary salts discussed in this section and in Section V may be represented by two or more canonical forms. Such resonance, where it occurs, is obvious and therefore only one of the structures is given.

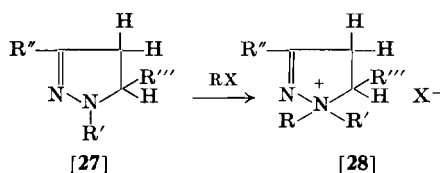
A. PYRAZOLE

Quaternary salt formation in a 1-substituted pyrazole ring (cf. **23**) can occur only at N-2 to give the fully resonance-stabilized symmetrical salt **24**. This reaction, which proceeds very readily, has been known for many years and therefore will not be commented on here.



Two ring systems derived from pyrazole have been studied more recently. The 4*H*-pyrazole ring (**25**) forms quaternary salts (**26**) with fair ease, and, as in the case of pyridazine (see Section IV, C), the direction of quaternization is controlled by the nature of R' and R".⁷⁴

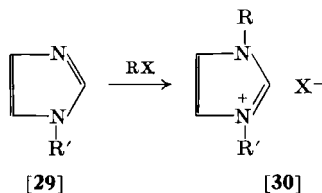
In the substituted 2-pyrazoline ring (**27**) both nitrogen atoms have lone pairs of electrons available; those on N-1 are no longer involved in an aromatic system, and in the two cases so far reported the salt



28 is formed. Thus, 3-amino-1-phenyl-2-pyrazoline gives **28** (R = Me, R' = Ph, R'' = NH₂, R''' = H, X = I, as shown by its alkaline degradation to 1-methyl-1-phenylhydrazine,⁷⁵ while 1,5-dimethyl-2-pyrazoline and methyl iodide yield **28** (R = R' = R''' = Me, R'' = H, X = I).⁷⁶

B. IMIDAZOLE

The formation of quaternary salts by the action of the common quaternizing reagents on 1-substituted imidazoles and benzimidazoles (**29**) to give salts of type **30** is well known. Only N-3 possesses a free



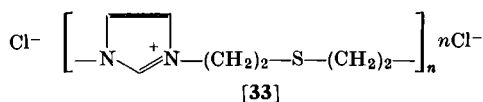
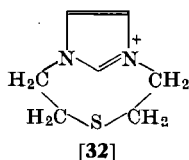
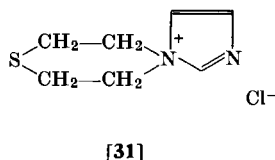
lone pair, and the high degree of symmetry of the resulting salt makes it normally very stable. There is, however, one case in which quaternization is said to take place in the other manner. Davis and Ross reacted 2,2'-dichlorodiethyl sulfide with imidazole and obtained a

⁷⁴ J. D. Kendall and G. F. Duffin, British Patent 730, 489 (1955).

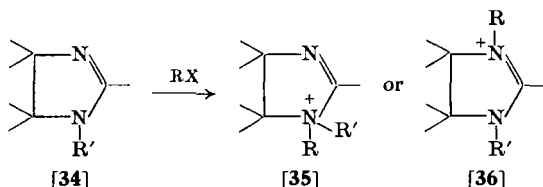
⁷⁵ G. F. Duffin and J. D. Kendall, *J. Chem. Soc.* 408 (1954).

⁷⁶ M. Lamchen, W. Pugh, and A. M. Stephens, *J. Chem. Soc.* 2429 (1954).

mono-quaternary salt for which all the evidence points to a compound with structure **31**.⁷⁷ The five-membered ring is no longer aromatic, and such a structure would be analogous to the hetero ring in the well-known *3H*-indoles. Alternative structures which are consistent with the authors' evidence are the *N,N'*-disubstituted salt **32**, which seems unlikely on stereochemical grounds, and a polymeric derivative (**33**); the molecular weight of the product was not reported.



The 4,5-dihydro compounds (**34**) might be expected to show different properties. Here, as with the pyrazolines discussed in Section IV, A, lone pairs of electrons should be available on both nitrogen atoms for reaction to give salts of type **35** and/or **36**. No salts of type **35** have been reported. Indeed, the reaction between the alkyl halide



and the 1-substituted 2-imidazoline is a very ready one⁷⁸; it is very difficult to stop the reaction between a *1H*-2-imidazoline and an alkylating reagent at the stage of the monosubstituted base **34**, and the quaternary salt **36** is the usual product.⁷⁹

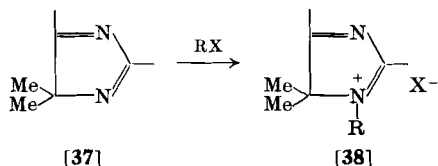
The *5H*-imidazole ring (**37**) possesses two nitrogen atoms with lone pairs available for quaternary salt formation, but unlike those in the

⁷⁷ S. B. Davis and W. F. Ross, *J. Am. Chem. Soc.* **69**, 1179 (1947).

⁷⁸ E. R. Shepherd and H. A. Shonle, *J. Am. Chem. Soc.* **69**, 2269 (1947).

⁷⁹ J. A. King and F. H. McMillan, *J. Am. Chem. Soc.* **68**, 1774 (1946).

corresponding 4*H*-pyrazole ring they are not similarly situated with regard to the ring structure. A variety of substituted 5*H*-imidazoles have been studied and in all cases the quaternization occurs at N-1 to



give **38**.⁸⁰ Salt formation is a fairly easy reaction even when the compound (cf. **37**) carries methylthio groups in both the 2- and 4-positions,⁸¹ whereas such substitution of other heterocyclic nuclei, for example 1,2,4-triazole,⁸² completely prevents quaternization under normal conditions.

C. PYRIDAZINE

The availability of many pyridazine derivatives and the current interest in applications of compounds containing that ring system have prompted many workers to study pyridazine quaternary salts. In general the quaternizing reaction proceeds with ease in this ring system,⁸³ as would be expected from its relatively high basicity; the pK_a of pyridazine is 2.33 as compared with values of 5.23 for pyridine, 0.6 for pyrazine, and 1.30 for pyrimidine.⁸⁴ This reactivity is illustrated by the violence with which the reaction between pyridazine and methyl iodide occurs in the absence of a solvent.⁸⁵ Since the two nitrogen atoms are in identical environments in the parent ring system, the position of quaternization is determined by the substituents.

A variety of 3,6-disubstituted pyridazines have been quaternized and the structures of the salts determined by unambiguous synthesis, degradation, or reactivity,^{86, 87} On the basis of these data the following

⁸⁰ J. D. Kendall and G. F. Duffin, British Patent 749,191 (1956).

⁸¹ J. D. Kendall and G. F. Duffin, British Patent 734,792 (1955).

⁸² G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *J. Chem. Soc.* 3799 (1959).

⁸³ R. L. Letsinger and R. Lasco, *J. Org. Chem.* **21**, 812 (1956).

⁸⁴ A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.* 2240 (1948).

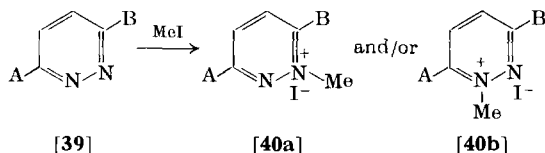
⁸⁵ R. L. Letsinger and R. Lasco, *J. Org. Chem.* **21**, 764 (1956).

⁸⁶ G. F. Duffin and J. D. Kendall, *J. Chem. Soc.* 3789 (1959).

⁸⁷ F. Halverson and R. C. Hirt, *J. Chem. Phys.* **49**, 711 (1951).

substituents can be placed in order of their activation of the quaternizing process: $\text{Me} > \text{H} > \text{Cl} > \text{SMe} > \text{Ph} > \text{OMe}$.

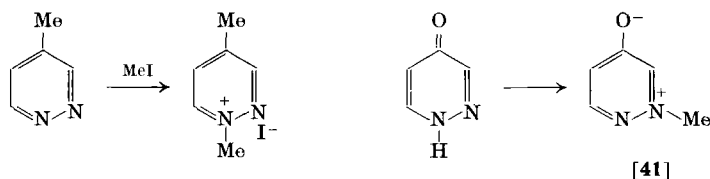
3-Amino-6-methylpyridazine (**39**; $\text{A} = \text{NH}_2$, $\text{B} = \text{Me}$) is reported to give the 2-salt (**40b**; $\text{A} = \text{NH}_2$, $\text{B} = \text{Me}$),⁸⁸ but the formation of such a



salt would seem at variance with the behavior of many similar compounds.

In the case of 6-methyl-3-methylthiopyridazine, a mixture of the two possible salts (cf. **40a** and **40b**) is formed,⁸⁶ but the detection of a small proportion of **40b** ($\text{A} = \text{MeS}$, $\text{B} = \text{Me}$), possibly 5%, depends on a delicate test which could not be applied to most of the other crude salts and therefore the formation of mixtures in other cases cannot be excluded. The possibility of the formation of mixtures does not appear to have been explored.

The directive influence of groups in the 4-position is shown by the quaternization in 4-methylpyridazine at N-1⁸⁹ and the reaction between 4-hydroxypyridazine and dimethyl sulfate to give a betaine (**41**).⁹⁰ Mason reported that quaternization of 4-hydroxypyridazine occurs at N-2.⁹¹



Attempts to prepare bis-quaternary salts from pyridazine and methyl iodide, ethyl bromide, or 1,4-dibromobut-2-ene were unsuccessful.⁹²

⁸⁸ S. F. Mason, *J. Chem. Soc.* 219 (1960).

⁸⁹ R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.* **76**, 2201 (1954).

⁹⁰ K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta* **39**, 1755 (1956).

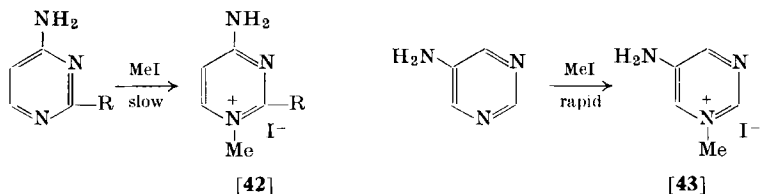
⁹¹ S. F. Mason, *J. Chem. Soc.* 674 (1958).

⁹² A. E. Blood and C. R. Noller, *J. Org. Chem.* **22**, 844 (1957).

D. PYRIMIDINE

In spite of much interest in the chemistry of pyrimidine, few of its simple derivatives, for example 4-methylpyrimidine, have been studied in detail, and, therefore, only a small number of simple pyrimidine quaternary salts have been reported.

4-Aminopyrimidine is the only monosubstituted derivative studied in which the position of quaternization is ambiguous. Methyl iodide and the 4-amino compound react slowly in 2-ethoxyethanol at 100° to give the N-1 salt ⁴⁰ (**42**; R = H), whereas 5-aminopyrimidine and



methyl iodide react in methanol in the same time in the cold ⁹³ to give **43**, and 2-aminopyrimidine and methyl iodide under the same conditions give the quaternary salt after some days.⁹⁴ Apparently the order of reactivity is 5-amino > 2-amino > 4-amino and the position of reaction parallels that of the corresponding quinazoline derivatives. 4-Amino-2-methylpyrimidine and methyl iodide⁹⁵ also react to give the N-1 salt (**42**; R = Me). The deactivating influence of the amino group is clearly indicated in the 4-derivative but is not present in the 5-compound. 4-Amino-2-chloropyrimidine also reacts with methyl iodide in 2-ethoxyethanol to give the 1-methyl salt **42** (R = Cl).⁹⁶

Apart from the two disubstituted compounds mentioned above, very few disubstituted pyrimidines appear to have been quaternized. The 4,6-dimethyl derivative, which can give only one mono-salt, reacts easily with methyl iodide.⁹⁷ Although the quaternization of 2,4-dimethylthiopyrimidine gives salts of unspecified structure, they have been used *en route* to the cyanine dyes⁹⁸; presumably reaction occurs at N-1. Treatment of 2,4-dimethoxypyrimidine with methyl

⁹³ N. Whittaker, *J. Chem. Soc.* 1565 (1951).

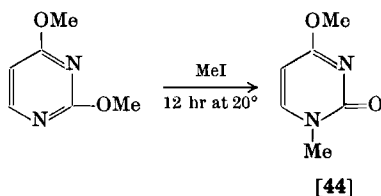
⁹⁴ D. J. Brown, E. Hoeger, and S. F. Mason, *J. Chem. Soc.* 4035 (1955).

⁹⁵ F. H. S. Curd and D. N. Richardson, *J. Chem. Soc.* 1853 (1955).

⁹⁶ F. H. S. Curd and D. N. Richardson, *J. Chem. Soc.* 1850 (1955).

⁹⁷ R. R. Hunt, J. F. W. McOmie, and F. R. Sayer, *J. Chem. Soc.* 525 (1959).

⁹⁸ J. D. Kendall, British Patent 425,609 (1935).



iodide at room temperature gave none of the expected methiodide but yielded instead 4-methoxy-1-methyl-2-pyrimidone (44)⁹⁹ by the usual type of decomposition of the 1-methiodide.

A wide range of 2,4,6-trisubstituted pyrimidines were quaternized by Curd *et al.*³⁹ during the Antricyde project, and the results are given in Table III. Apart from the possible steric effect of the anilino group,

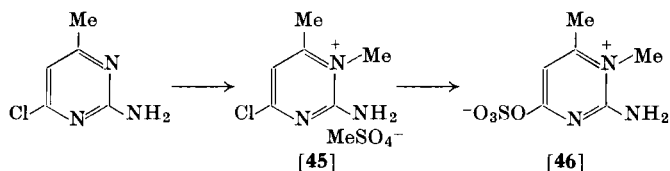
TABLE III
QUATERNIZATION OF PYRIMIDINES

Substituted pyrimidine	Quaternizing reagent	Position of quaternization		Reference
		Principal product	Subsidiary product	
6-Chloro-2-methyl-4-methylthio-	Me ₂ SO ₄ in PhNO ₂	1	3	40
4-Anilino-6-chloro-2-methyl-	Me ₂ SO ₄ in PhNO ₂	1	none	40
6-Amino-4-chloro-2-methyl-	MeI in EtO·CH ₂ CH ₂ OH	3	1	95
4-Amino-2-chloro-6-methyl	MeI in EtO·CH ₂ CH ₂ OH	1	none	96
4-Amino-6-methyl-2-methylthio-	MeI in MeOH	1	none	96
2-Amino-6-anilino-4-methyl-	MeI in MeOH	3	none	39
2-Amino-6-chloro-4-methyl-	MeI in EtO·CH ₂ CH ₂ OH	3	1	39
2-Amino-6-chloro-4-methyl-	Me ₂ SO ₄ in PhNO ₂ at 50°	3	none	39
2-Amino-6-chloro-4-methyl-	Me ₂ SO ₄ in PhNO ₂ at 110°	3	1	39

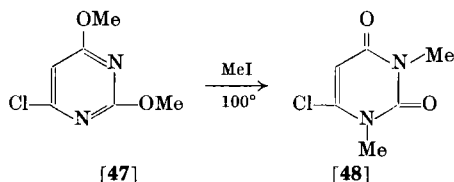
⁹⁹ G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 2001 (1930).

it is possible to make the following generalizations from these data: (1) The activation effect of substituents on quaternization is in the order $\text{Me} > \text{Cl} > \text{SMe} > \text{NH}_2$, (2) a substituent exerts a smaller effect when it is in the 2-position than when it is in the 4- or 6-position, and (3) the deactivating influence of an amino or a methylthio group is less effective at the remote nitrogen atom than at the adjacent one. The comparison of the 2- and 4-substituents is similar to that for simple 2- and 4-aminopyrimidines mentioned above. All of these effects are to be expected if it is primarily an inductive effect which is operative, as has been suggested for pyridazine derivatives.⁸⁶

It is also interesting to note that quaternization of a chloropyrimidine at the nitrogen atom adjacent to the chloro group with methyl iodide results in the easy replacement of the chlorine by iodine, whereas similar salt formation on the remote nitrogen either leaves the chlorine unaffected or replacement occurs only at higher temperatures.³⁹ A similar reaction occurs between 2-amino-6-chloro-4-methylpyrimidine and dimethyl sulfate in nitrobenzene to give the salt **45** and betaine **46**.⁴⁰



5-Methyl and 6-methyl-5-*n*-propyl substituted 2,4-dimethoxypyrimidines react with methyl iodide, as does the simple dimethoxy compound, to give methoxypyrimidones,^{100, 101} but the 6-chloro-2,4-dimethoxy derivative (**47**) is affected only at 100° , when it gives 4-chloro-1,3-dimethyluracil (**48**).¹⁰²



2,4,6-Trimethoxypyrimidine reacts very slowly with methyl iodide to give the methoxy-dimethyluracil.¹⁰⁰ Although no quaternary salts

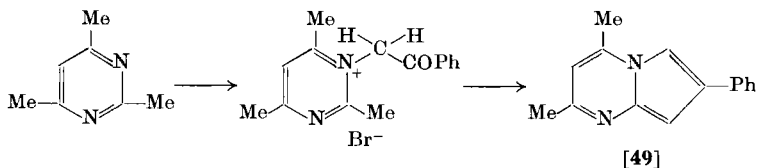
¹⁰⁰ W. Schmidt-Nickels and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 4511 (1930).

¹⁰¹ Y.-F. Chi, S.-S. Wei, and M.-S. Liang, *J. Am. Chem. Soc.* **61**, 3377 (1939).

¹⁰² H. J. Fisher and T. B. Johnson, *J. Am. Chem. Soc.* **54**, 728 (1932).

are isolated from the reactions of these methoxy compounds such salts must be intermediates in the reactions; here again the inductive effect of the substituents appears to be operating, the methoxy groups retarding the reaction.

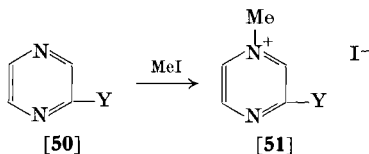
2,4,6-Trimethylpyrimidine and phenacyl bromide give a salt which on further heating ring-closed to **49**, but 2,4-dimethylpyrimidine does not react with phenacyl bromide.¹⁰³



Cyanine dyes have been prepared from the salts obtained by the quaternization of 4,6-dimethyl-2-phenylpyrimidine¹⁰⁴ and 2-alkyl- or 2-aryl-4,6-dimethylthiopyrimidines,¹⁰⁵ but there can be no ambiguity in the structure of these quaternary salts.

E. PYRAZINE

The quaternization of pyrazine compounds has not been extensively studied, and, therefore, a detailed discussion of the effect of substituents is not possible. Recently Cheeseman¹⁰⁶ has shown, from spectroscopic evidence, that 2-amino- and 2-diethylamino-pyrazine (**50**, Y = NH₂ and NEt₂) quaternize at N-4, although protonation occurs at position-1. Other substituted pyrazines from which quaternary salts of structure **51** are formed include 2-chloro-²¹ and 2-



¹⁰³ E. Ochiai and M. Karii, *J. Pharm. Soc. Japan* **59**, 18 (1939); *Chem. Abstr.* **33**, 3791 (1939).

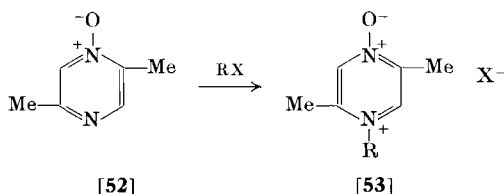
¹⁰⁴ L. G. S. Brooker, W. F. Holcomb, and C. K. Banks, U.S. Patent 2,472,565 (1946).

¹⁰⁵ Kodak Ltd., British Patent 823, 943.

¹⁰⁶ G. W. H. Cheeseman, *J. Chem. Soc.* 242 (1960).

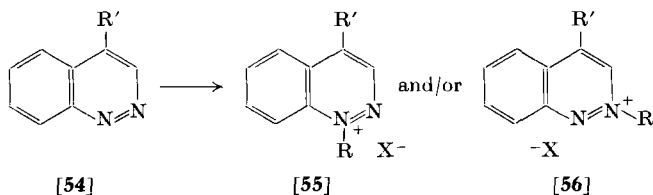
carbamoyl compounds.¹⁰⁷ Quaternization at N-4 would be expected in the latter two compounds because of the electronic effect of the 2-substituents, but the behavior of 2-aminopyrazine, in conjunction with that of many other amino-heterocyclics, suggests that inductive rather than mesomeric effects are operative.

2,5-Dimethylpyrazine 1-oxide (**52**) does not appear to react at the exocyclic oxygen with methyl iodide or benzyl chloride but instead reacts at N-4 to form the quaternary salt **53**.¹⁰⁸



F. CINNOLINE

The quaternization of the cinnoline ring is of considerable interest because it is present in some biologically active substances, in particular the dimethiodide of di-(4-amino-6-cinnolyl)-guanidine, which shows trypanocidal activity.¹⁰⁹ Further, cinnolines are of theoretical interest since they contain nitrogen atoms corresponding to those of both quinoline and isoquinoline. The question as to which nitrogen atom is involved in the reaction remains unresolved in spite of a large amount of work by Simpson *et al.* The most positive evidence, apart from calculations which show that N-1 in cinnoline is the more basic



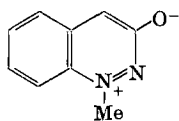
¹⁰⁷ S. Kushner, H. Dalalian, J. L. Sanjurjo, F. L. Bach, Jr., S. R. Safir, V. K. Smith, Jr., and J. H. Williams, *J. Am. Chem. Soc.* **74**, 3617 (1952).

¹⁰⁸ C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.* **23**, 1603 (1958).

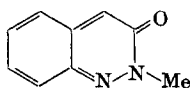
¹⁰⁹ J. R. Keneford, E. M. Lourie, J. S. Morley, J. C. E. Simpson, J. Williamson, and P. H. Wright, *J. Chem. Soc.* 2595 (1952).

nitrogen,¹¹⁰ is obtained from 4-substituted derivatives of cinnoline (cf. **54**). The methiodide of cinnoline itself, apparently a homogeneous substance, does not yield 1-methyl-4-cinnolone on treatment with alkali and ferrieyanide, the classic procedure used to oxidize many quaternary salts. No identifiable product was isolated, but treatment of cinnoline methiodide with alkali under nitrogen at room temperature gave an unidentified basic product which was not purified. The formation of 1-methylindole in low yield by hydrogenation of cinnoline methiodide in the presence of Raney nickel points, but not conclusively, to structure **55** ($R = \text{Me}$, $R' = \text{H}$) for that salt.¹¹¹

The methiodide and ethiodide of 4-methylcinnoline possess methyl groups which condense easily with aldehydes,^{112, 113} and even with ethyl orthoformate,¹¹⁴ to give polymethine derivatives. These reactions, particularly that with the ortho ester, suggest that the salts have structure **55** ($R = \text{Me}$ or Et , $R' = \text{Me}$). The methiodide of 3-methylcinnoline also reacts with aldehydes, although more slowly,¹¹⁵ but no reaction with ethyl orthoformate has been reported. Although **55** ($R' = \text{Me}$) appears to be the most likely structure for the product, the 4-methyl group may direct the quaternization on N-1¹¹² and, therefore, the position of quaternization may be different with other cinnoline derivatives.



[57]



[58]

The action of dimethyl sulfate on 3-hydroxycinnoline can give two different products.¹¹⁵ In the presence of excess alkali a low yield of an orange product was obtained, for which the zwitterionic structure **57** was tentatively advanced, but with insufficient alkali the product is 2-methyl-3-cinnolone (**58**). The formation of **57** parallels the formation of the betaine (**41**) from 4-hydroxypyridazine.⁹⁰

The 4-aminocinnolines have been extensively studied. In a key

¹¹⁰ H. C. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.* 971 (1949).

¹¹¹ C. M. Atkinson and A. Taylor, *J. Chem. Soc.* 4236 (1955).

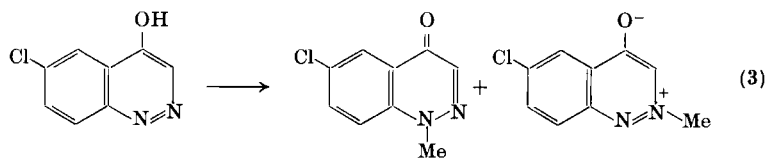
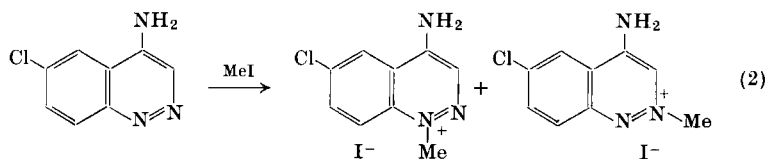
¹¹² C. M. Atkinson and J. C. E. Simpson, *J. Chem. Soc.* 808 (1947).

¹¹³ J. D. Kendall and D. J. Fry, British Patent 698,575 (1953).

¹¹⁴ A. B. Tal, *J. Indian Chem. Soc.* **36**, 64 (1959); *Chem. Abstr.* **53**, 21983 (1959).

¹¹⁵ E. J. Alford and K. Schofield, *J. Chem. Soc.* 1811 (1953).

paper, Simpson¹¹⁶ described the treatment of 4-amino-6-chlorocinnoline with methyl iodide to produce a salt identified as the 1-methiodide because it could be converted by alkali into 6-chloro-1-methyl-4-cinnolone; the latter compound was prepared by methylation of 6-chloro-4-hydroxycinnoline but has not been unambiguously synthesized. A second product, which was isomeric with the presumed 6-chloro-1-methyl-4-cinnolone, was present in the mixture obtained by alkaline hydrolysis of the methiodide. Also, methylation of the 4-hydroxycinnoline gave a second product which was difficult to purify. It seems possible that both the quaternization and methylation gave mixtures of products formed by reactions at both nitrogen atoms, as was discovered later with the 4-amino-6-nitro- and 4-amino-7-chloro-compounds.^{111, 117} If this is the case [cf. Eqs. (2) and (3)],



it is not possible without other evidence to allocate structures to the salts or methylated derivatives. The formation of the zwitterion seems quite likely in view of the behavior of 4-hydroxypyridazine.⁹⁰ A variety of 4-aminocinnolines, including the 6- and 8-nitro compounds were also converted into their salts, and these were believed to be N-1 derivatives.¹⁰⁹ It is noteworthy that 4-amino-3-methyl-8-nitrocinnoline was very difficult to quaternize.

Atkinson and Taylor¹¹¹ summarized the evidence in support of the earlier assumption, arising from the evidence discussed above, that quaternization occurs on N-1 and also showed that 4-amino-, 4-amino-6-nitro-, and 4-amino-7-chloro-cinnoline gave two salts with methyl iodide, while 4-amino-8-nitrocinnoline gave only one salt and the

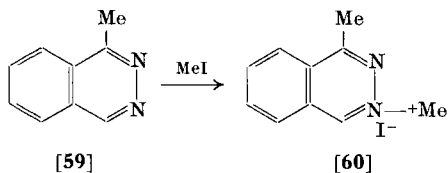
¹¹⁶ J. C. E. Simpson, *J. Chem. Soc.* 1653 (1947).

¹¹⁷ J. R. Keneford, J. S. Morley, J. C. E. Simpson, and P. H. Wright, *J. Chem. Soc.* 2601 (1952).

4-acetamido-8-nitro compound would not quaternize. These salts were classified by differences in their adsorption spectra as α - and β -salts. The possibility that the exocyclic amino group was involved was removed by showing that ammonia, not methylamine, was produced by hydrolysis and that 4-methylaminocinnoline hydriodide was different from either product obtained by the reaction of 4-aminocinnoline with methyl iodide. Acetylation of the α -salt from 4-aminocinnoline gave the same product as was obtained by direct quaternization of the 4-acetamidocinnoline. The hydrolysis products obtained from each of the salts were studied and their structures related to the 1-methyl-4-cinnolones, but in some cases no pure product could be isolated. The balance of the evidence indicates that 4-aminocinnolines probably quaternize mainly on N-1 to give the α -salts. It should, however, be noted that the β -salt from 4-amino-6-nitrocinnoline gives the compound described as 1-methyl-6-nitro-4-cinnolone while the 8-nitro analog, which for steric reasons is believed to be the N-2 salt, gives 4-hydroxy-8-nitrocinnoline, and, therefore, it would appear most important to prepare the reference methylated derivatives unambiguously. (See Note Added in Proof, p. 56.)

G. PHTHALAZINE

Although there has been interest recently in phthalazine quaternary salts, no work has been reported on the position of quaternization since the classic studies of Gabriel and co-workers.^{118, 119} For the sake of completeness, it may be noted that 4-methylphthalazine (**59**) and methyl iodide gave the salt **60**; alkaline degradation of **60** gave a

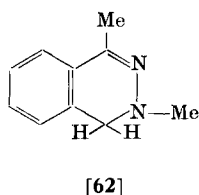
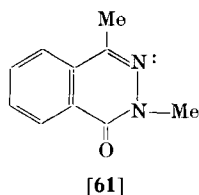


mixture of 1,3-dimethyl-4-phthalazone (**61**) and 1,3-dimethyl-3,4-dihydrophthalazine (**62**). Compound **61** was also obtained by methylation of 1-methyl-4-phthalazone, and the structure (**60**) seems well-established. The behavior of 4-methylphthalazine differs from that

¹¹⁸ S. Gabriel and F. Müller, *Ber.* **28**, 1830 (1895).

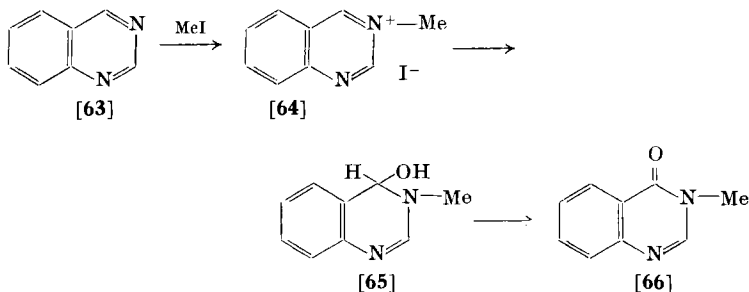
¹¹⁹ S. Gabriel and G. Eschenbach, *Ber.* **30**, 3022 (1897).

of the related 3-methylpyridazine,⁸⁶ therefore a steric effect must be operating in the phthalazine compound.



H. QUINAZOLINE

The methiodide of quinazoline (**63**) was studied by Gabriel and Colman¹²⁰ and shown to possess structure **64**. Gabriel's evidence has been checked by later workers^{121, 122} and the substitution in the 3-position proved beyond all doubt, for example, by conversion *via* the pseudo base **65** into 3-methyl-4-quinazolinone (**66**).⁵¹ It is significant



that the methiodide was obtained by Gabriel only as the methanolate, although Fry *et al.*⁵¹ were able to obtain the salt in its pure form as a deliquescent solid; it seems likely that the very common addition (of solvent) across the 3,4-bond of quinazoline is again in evidence.

Morley and Simpson prepared quaternary salts from 4-phenoxyquinazoline and 6- and 7-nitro-derivatives of 4-anilino- and 4-acetamidoquinazoline.^{123, 124} 6-Nitro-4-aminoquinazoline, however, could not be quaternized under the fairly mild conditions used by the

¹²⁰ S. Gabriel and J. Colman, *Ber.* **37**, 3643 (1904).

¹²¹ A. R. Osborn and K. Schofield, *J. Chem. Soc.* 3977 (1956).

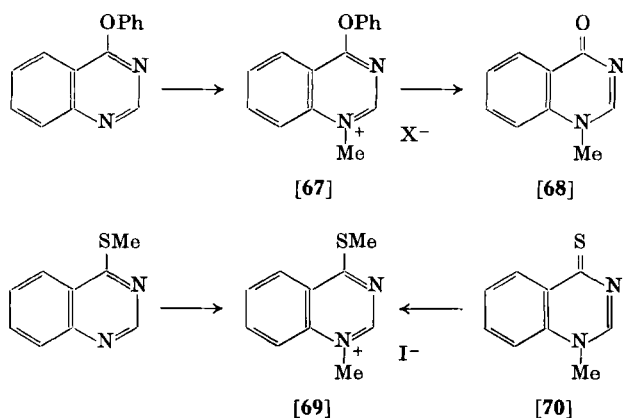
¹²² C. Schöpf and F. Oechler, *Ann. Chem.* **523**, 1 (1936).

¹²³ J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.* 1354 (1949).

¹²⁴ J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.* 360 (1948).

investigators, and, as was found later, fusion with methyl toluene-*p*-sulfonate at 140° was to effect necessary quaternization.⁴³ These salts of the 4-substituted quinazolines were formed by quaternization at N-1; for example, the product (67) from 4-phenoxyquinazoline and methyl toluene-*p*-sulfonate gave 1-methyl-4-quinazalone (68) on treatment with alkali.¹²³

Fry *et al.*⁵¹ prepared quaternary salts from 4-methyl- and 4-methylthio-quinazoline and found that the same cyanine dyes were obtained by suitable reactions of either salt. An unambiguous synthesis of the 4-methylthio salt (69) from 1-methylquinazoline-4-thione (70) proved that both of the salts carried groups on N-1.



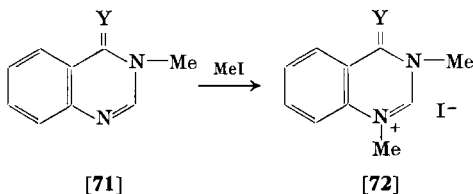
It appears, therefore, that quaternization of the unsubstituted quinazoline nucleus is the exception and that steric factors probably cause the substituted derivatives to react at the 1-position. 8-Hydroxyquinazoline is believed also to quaternize at the 1-position; here the effect of the hydroxyl group would be to reduce any tendency towards reaction at the 1-position and it is interesting that a monoalcoholate is isolated in this case too.¹²⁵

4-Methoxyquinazoline and methyl iodide give the salt 72 ($Y = O$),¹²⁶ and, although the route for this reaction has not been investigated, there is a suggestion that the reaction occurs at N-3. A final decision concerning the nature of electronic and steric influences on quaternization in the quinazoline ring must clearly await further work.

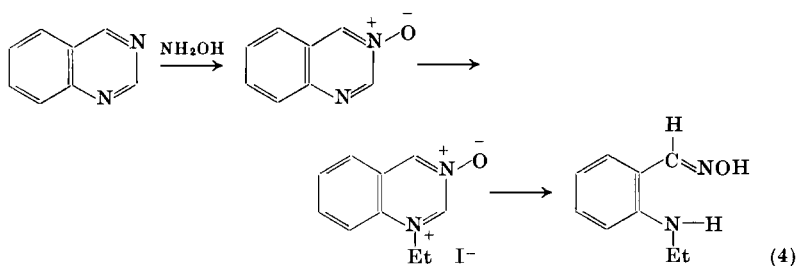
¹²⁵ A. Albert and A. Hampton, *J. Chem. Soc.* 505 (1954).

¹²⁶ M. T. Bogert and G. A. Geiger, *J. Am. Chem. Soc.* **34**, 683 (1912).

The quinazoline ring also gives some anomalous quaternization reactions, which presumably reflect the influence of the unusual 3,4-bond. 3-Methyl-4-quinazolone (**71**; Y = O)^{123, 126} and, more surprisingly, 3-methylquinazoline-4-thione (**71**; Y = S)⁵¹ react at N-1 to give the salts **72** (Y = O) and **72** (Y = S), respectively. Apparently the usual mesomeric shift of the =N-C=S group is insufficient to outweigh the normal nucleophilicity of the N-1 atom.



Quaternary salt formation in 4-quinazoline 3-oxide and its 4-amino and 4-methyl derivatives has been studied by Adachi.¹²⁷ These N-oxides, prepared by reaction of the simple quinazoline with hydroxylamine, react with ethyl iodide at N-1, although only in the case of the 4-amino derivative could the ethiodide be purified. The salts are degraded by alkali yielding derivatives of ethylaniline [Eq. (4)].



I. QUINOXALINE

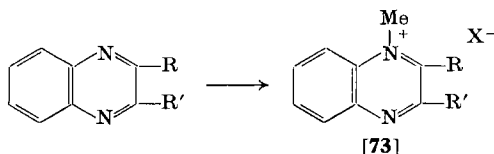
Quinoxaline and many of its derivatives are easily converted into quaternary salts, but the use of mild conditions for extended times is usually preferable to drastic conditions, which tend to give brown or green amorphous solids.²⁵

2-Phenylquinoxaline has been shown to quaternize on N-4,¹²⁸ as

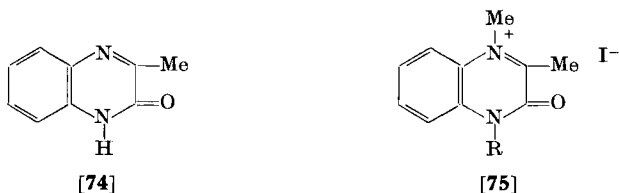
¹²⁷ K. Adachi, *Yakugaku Zasshi* **77**, 507 (1957); *Chem. Abstr.* **51**, 14745 (1957).

¹²⁸ J. Druey and A. Hüni, *Helv. Chim. Acta* **35**, 2301 (1952).

does 2-acetamidoquinoxaline,¹²⁹ to give **73** ($R = H$, $R' = Ph$) or **73** ($R = H$, $R' = NHAc$), respectively. The acetamido salt was formed by allowing the base and methyl toluene-*p*-sulfonate to react at 110° for 30 min, but 2-aminoquinoxaline rapidly gave intractable tars under the same conditions and the use of milder conditions has not been



reported. Methyl iodide and 3-methyl-2-phenylquinoxaline have been reported to give a crude salt which yields cyanine dyes but does not possess a reactive methyl group after purification.¹³⁰ This suggests that the main product is that arising from quaternization on the ring-nitrogen atom adjacent to the phenyl group, i.e. **73** ($R = Ph$, $R' = Me$), and that only a small proportion of the isomeric salt (**73**; $R = Me$, $R' = Ph$) is formed. Unfortunately, no experimental evidence is given to support these observations, but it seems unlikely that the quaternization would take that direction since the steric effect of the phenyl group is relatively strong.



3-Methyl-2-quinoxalone (**74**) and its 1-methyl and 1-phenyl derivatives have been shown to quaternize under drastic conditions, with dimethyl sulfate at 140° , to give N-4 salts (**75**) which possess a reactive methyl group.¹³¹ Similarly 2-quinoxalones containing a 3-styryl group are also believed to quaternize under stringent conditions on the N-4 atom.¹³²

¹²⁹ C. M. Atkinson, C. W. Brown, and J. C. E. Simpson, *J. Chem. Soc.* 26 (1956).

¹³⁰ A. H. Cook, J. Garner, and C. A. Perry, *J. Chem. Soc.* 710 (1942).

¹³¹ A. H. Cook and C. A. Perry, *J. Chem. Soc.* 394 (1943).

¹³² S. Bodforss, *Ann. Chem.* **609**, 103 (1957).

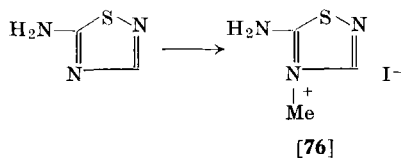
A number of quinoxalines carrying substituents in the benzene ring base have been quaternized, including 5-ethoxy,¹³³ 6-methyl, 6-chloro,²⁵ and some 2-phenyl derivatives,^{128, 134} but in none of these cases has the position of quaternization been ascertained. 5-Hydroxy-quinoxaline gives a methiodide which can still form metal complexes, indicating that salt formation occurred on N-1.¹²⁵

Analogous to other N-oxides of polynitrogen heterocyclic bases, quinoxaline 1-oxide¹³⁵ and phenazine 9-oxides⁴⁴ undergo quaternization at N-4 and N-10, respectively.

J. THIADIAZOLES

1. 1,2,4-Thiadiazole

The structure of only one 1,2,4-thiadiazole salt has been determined. Unambiguous synthesis of the imino compound obtained on alkali treatment of the salt formed by the reactions of methyl iodide with 5-amino-1,2,4-thiadiazole established that the salt possesses structure **76**.¹³⁶ This quaternization exactly parallels the reaction occurring in



1,2,4-triazole (see Section IV, K), in which case an —NR group replaces the ring sulfur atom, and presumably similar electronic effects are operative.

2. 1,3,4-Thiadiazole

Interest in 1,3,4-thiadiazole salts has been stimulated by their use as intermediates for the preparation of cyanine dyes. 2,5-Dimethyl-1,3,4-thiadiazole **77** (R = R' = Me) reacts readily with methyl iodide.¹³⁷ 2-Methyl-5-phenyl and 5-phenyl-1,3,4-thiadiazole quaternize fairly easily on the nitrogen atom furthest from the phenyl

¹³³ W. K. Easley and M. X. Sullivan, *J. Am. Chem. Soc.* **74**, 4450 (1952).

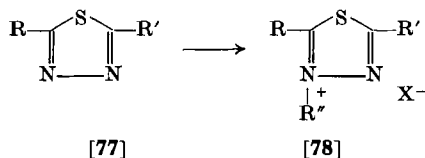
¹³⁴ A. Dornow and W. Sassenberg, *Ann. Chem.* **594**, 185 (1955).

¹³⁵ J. K. Landquist, *J. Chem. Soc.* 2816 (1953).

¹³⁶ J. Goerdeler, A. Huppertz, and K. Weimber, *Chem. Ber.* **87**, 68 (1954).

¹³⁷ M. Ohta and H. Kimoto, *J. Pharm. Soc. Japan* **76**, 10 (1956); *Chem. Abstr.* **50**, 12992 (1956).

group to give **77** ($R = \text{Me}$, $R' = \text{Ph}$) and **78** ($R = \text{H}$, $R' = \text{Ph}$), respectively.¹³⁸ These structures were deduced from the high reactivity of the 2-methyl group, which condenses even with ethyl orthoformate, in the 2-methyl salt, and from a classic cyanine condensation between the 2-methyl and the 2-hydrogen quaternary salts to give the monomethine cyanine.¹³⁸

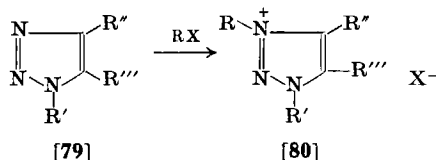


Ethyl iodide and 5-amino-2-methyl-1,3,4-thiadiazole react at 110° to give the N-3 salt (**78**; $R = \text{Me}$, $R' = \text{NH}_2$, $R'' = \text{Et}$), as shown by the presence of the very reactive methyl group; this salt is also used to prepare cyanine dyes.¹³⁹ The slow quaternization at the ring-nitrogen atom furthest from the amino group is consistent with the reactions observed in other ring systems. As would be expected, 5-alkylthio-2-methyl-1,3,4-thiadiazoles form salts at the N-3 (**78**; $R = \text{Me}$, $R' = \text{S-alkyl}$).¹⁴⁰

K. TRIAZOLES

1. 1,2,3-Triazole

In a 1-substituted 1,2,3-triazole (**79**), both the 2- and 3-nitrogen atoms possess lone pairs of electrons that are available for quaternary salt formation, and quaternization is known to occur at the 3-nitrogen atom to give the symmetrical cation (**80**). Thus, the reaction between 1-methyl-1,2,3-triazole and benzyl iodide yields the same salt as is obtained from the interaction of 1-benzyl-1,2,3-triazole and methyl iodide¹⁴¹; the salt must therefore be **80** ($R = \text{Me}$, $R' = \text{PhCH}_2$,



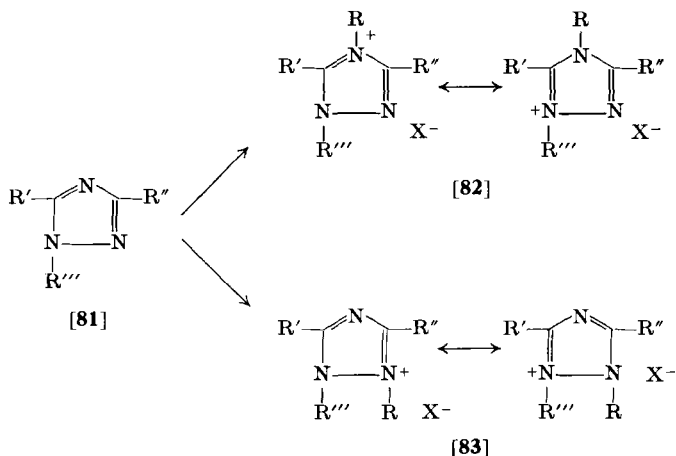
¹³⁸ M. Ohta, *J. Pharm. Soc. Japan* **73**, 1127 (1953); *Chem. Abstr.* **48**, 12091 (1954).

¹³⁹ A. W. Anish and C. A. Clark, U.S. Patent 2,500,112 (1946).

¹⁴⁰ G. F. Duffin, D. J. Fry, and J. D. Kendall, British Patent 785,939 (1957).

¹⁴¹ R. H. Wiley and J. Moffat, *J. Am. Chem. Soc.* **77**, 1703 (1955).

$R'' = R''' = H$, $X = I$). Similarly, 1-phenyl-1,2,3-triazole and ethylene sulfonyl chloride react at N-3 and at the *beta*-carbon atom, respectively, to give the betaine **79** ($R = Ph$, $R' = CH_2\bar{C}HSO_2Cl$, $R'' = R''' = H$), which then reacts with water to give the sulfonate betaine (**80**; $R = Ph$, $R' = -CH_2CH_2SO_3^-$, $R'' = R''' = H$).¹⁴² Methyl iodide and 1,5-dimethylbenzotriazole yielded **80** ($R = R' = Me$, $X = I$, and R'' and R''' form a methylbenzo ring).¹⁴³



2. 1,2,4-1*H*-Triazole

This nucleus (**81**) also possesses two nitrogen atoms, i.e. N-2 and N-4, with lone pairs of electrons that are available for quaternization, and in this case salt formation at either of these atoms would yield products for which two canonical forms can be written. These forms are shown in structures **82** and **83**. Although mesomerism appears to be more extended between the two nitrogen atoms of formula **83**, which led to the suggestion¹⁴⁴ that such a salt is more likely to be formed than one of structure **82**, no salts of type **83** have been prepared by direct quaternization; all those obtained in this manner have structure **82**. 1,2,4-Triazoles carrying a variety of substituents, including 1-aryl and -alkyl groups and alkyl and alkylthio substituents in the 3- and 5-positions, react with methyl iodide to give

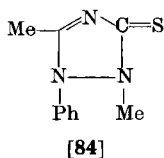
¹⁴² C. S. Rondestvedt and P. K. Chang, *J. Am. Chem. Soc.* **77**, 6532 (1955).

¹⁴³ F. Krollpfeiffer, A. Rosenberg, and C. Müllhausen, *Ann. Chem.* **515**, 119 (1935).

¹⁴⁴ M. R. Atkinson and J. B. Polya, *Chem. Ind. (London)* 462 (1954).

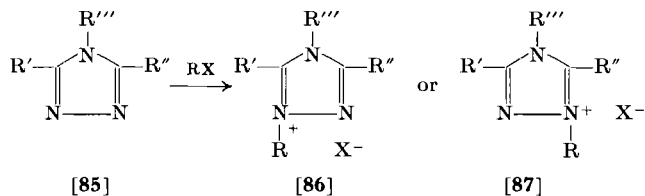
the 4-methyl salts.⁸¹ The structure of 1,3,4,5-tetramethyl-1,2,4-triazolium iodide was proved by its formation from either 1,3,5-trimethyl-1,2,4-triazole or 3,4,5-trimethyl-4,1,2-triazole (see next section), while the structure of the methiodide formed by the 1-phenyl-3,5-dimethyl compound was shown to be **82** ($R = R' = R'' = \text{Me}$, $R''' = \text{Ph}$) by alkaline degradation to phenylhydrazine and methylamine. It will be noted that this position for the quaternization accords with values quoted for the electron density of the triazole molecule.¹⁴⁵

The only triazole salt of type **83** that has been reported⁸² was obtained by the reaction of 2,3-dihydro-2,5-dimethyl-1-phenyl-1,2,4-triazole-3-thione (**84**) with methyl iodide to give **83** ($R = R' = \text{Me}$, $R''' = \text{Ph}$, $R'' = \text{MeS}$).



3. 4,1,2-Triazole

This ring system **85** which exhibits the symmetry common to many nitrogen-containing heterocycles, has two nitrogen atoms identically situated from the point of view of the ring, and the position of substitution is controlled entirely by the substituents R' and R'' . The electronic effects exhibited parallel those shown by pyridazine (cf. Section IV, C). The general reactivity of the 1,2,4- and 4,2,1-triazole rings towards quaternizing reagents is very similar. An unusual type of substituent effect is observed in the 4,1,2-triazole **85** ($R'' = R''' = \text{H}$, $R' = p$ -dimethylaminophenylazo), which may also be considered as its tautomer, the corresponding 1,2,4-triazole. On reaction with excess methyl sulfate, **85** gives the salt **86** ($R = R''' = \text{Me}$,

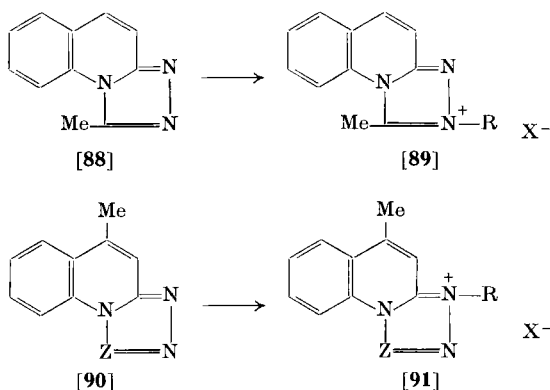


¹⁴⁵ M. R. Atkinson and J. B. Polya, *J. Chem. Soc.* 141, 3319 (1954).

$R'' = H$, $R' = p$ -dimethylaminophenylazo),¹⁴⁶ quaternization having taken place at the nitrogen nearest the azo linkage rather than at the nitrogen adjacent to the hydrogen (cf. **87**).

4. Fused Triazoles

Two interesting cases of quaternary salt formation are illustrated by compounds **88** and **90** ($Z = CH$) which contain fused quinoline and triazole rings. In these compounds both of the nitrogen atoms unique to the triazole ring possess lone pairs of electrons which are available for reaction. With compound **88** reaction occurs to give **89**,¹⁴⁷ but in



compound **90** ($Z = CH$) the nitrogen adjacent to the quinoline residue is attacked to give **91**.¹⁴⁸ In the absence of a steric counter-effect, which would not be expected to be pronounced in bases of these types, the inductive effect of the methyl groups in the two different positions is apparently sufficient to cause the observed results. The benzothiazole analog of **88** behaves in a similar manner.¹⁴⁹

L. TETRAZOLES

Although the formation of tetrazolium salts of structure **92** by the oxidation of formazans under acid conditions has been known for many years,¹⁵⁰ it is only recently that the quaternization of 1,5-disubstituted

¹⁴⁶ Badische Anilin and Soda Fabrik, British Patent 837,471 (1957).

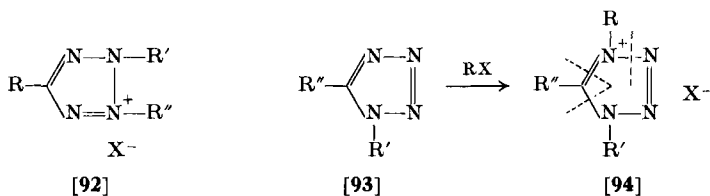
¹⁴⁷ Kodak Ltd., British Patent 783,021 (1957).

¹⁴⁸ Kodak Ltd., British Patents 736,266 (1955) and 782,311 (1957).

¹⁴⁹ Kodak Ltd., Belgian Patent 558,627 (1958).

¹⁵⁰ A. W. Nineham, *Chem. Rev.* **55**, 355 (1955).

tetrazoles (**93**) by, for example, methyl iodide has been shown to give salts of type **94**.^{151, 152} The structure of these salts was established by alkaline degradation of the methiodide of 5-methyl-1-phenyltetrazole to phenyl azide and methylamine, the hydrolysis having occurred at the sites indicated by dotted lines on structure **94**; the salt must therefore be **94** ($R' = \text{Ph}$, $R = R'' = \text{Me}$, $X = \text{I}$).



In the same way, 1-substituted-5-aminotetrazoles react with benzyl chloride to give 1-substituted 4-benzyl-5-iminotetrazolines.¹⁵³

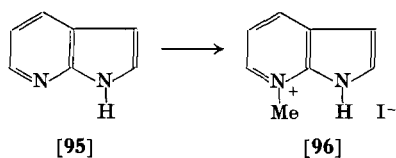
Compounds containing a fused quinoline-tetrazole ring system (**90**; $Z = \text{N}$) behave similarly to compounds containing the simple tetrazole ring and give salts of type **91** ($Z = \text{N}$).^{147, 148}

V. The Position of Quaternization in Compounds with Two or More Nitrogen-Containing Rings

A. DIAZAINDENES AND RELATED COMPOUNDS

1. *Aza-indoles*

The introduction of a nitrogen atom into the benzene ring of indole affords a center, not present in indole itself, at which quaternary salt formation occurs readily, and the base **95** is converted into a quaternary salt (**96**) on the pyridine-type nitrogen atom.¹⁵⁴



¹⁵¹ F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Am. Chem. Soc.* **73**, 4457 (1951).

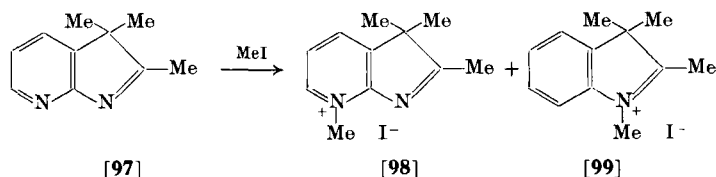
¹⁵² G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind. (London)* 1355 (1955).

¹⁵³ R. M. Herbst and K. G. Stone, *J. Org. Chem.* **22**, 1139 (1957).

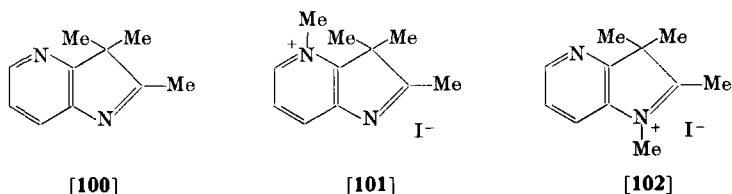
¹⁵⁴ M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.* **77**, 6554 (1955).

In the case of the aza derivatives of the 3*H*-indole or indolenine ring, however, the two nitrogen atoms would be expected to be more nearly equivalent, indolenine itself being easily converted into its quaternary salt. The quaternization reactions of 1,7-, 1,5-, and 1,4-diaza-3,3-dimethyl-3*H*-indenenes have recently been studied by Ficken and Kendall.

The 1,7-diazaindene **97** reacts with methyl iodide to give a mixture of the salts **98** and **99**.¹⁵⁵ Salt **98** is clearly the main product because it was the only compound obtained pure on recrystallization of the crude



mixture. By allowing the crude mixture of the two salts to condense with *p*-dimethylaminobenzaldehyde (both of the salts possess reactive methyl groups) and then separating the resultant dyes chromatographically, the ratio of **98** to **99** was shown to be 9:1. As would be expected,¹⁵⁶ both of the nitrogen atoms in the base are less basic (as shown by the Brooker deviations of the derived cyanine dyes¹⁵⁷) than those in pyridine or indolenine, and this is reflected in the fairly slow rate of quaternization.



The 1,4-diaza compound **100**,¹⁶⁸ however, behaves quite differently and yields the salt **102** as the only isolatable product. The question of the presence or absence of the alternative salt (**101**) cannot be settled as easily as in the case of the 1,7-diazaindene **97** because **101** would not

¹⁵⁵ G. E. Ficken and J. D. Kendall, *J. Chem. Soc.* 3202 (1959).

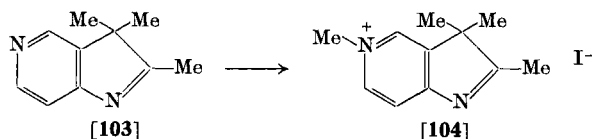
¹⁵⁶ A. Albert, *Chem. Soc. (London), Spec. Publ. No. 3*, 124 (1955).

¹⁵⁷ L. G. S. Brooker and R. A. Spague, *J. Am. Chem. Soc.* **67**, 1869 (1945).

¹⁵⁸ G. E. Ficken and J. D. Kendall, *J. Chem. Soc.* 584 (1961).

contain a reactive methyl group; the carbanion formed by the removal of a proton for the 2-methyl group would not be stabilized by charge delocalization on a quaternary nitrogen atom. The position of quaternization was settled by unambiguous synthesis of **102** and by the observation that the product of quaternization possesses a reactive methyl group. The presence of some of the product (**101**) in which quaternization occurred on the pyridine-nitrogen was inferred because the yield of (**102**) was only 50%. The authors suggested that the marked difference in behavior between the 1,7- and 1,4-diaza compounds is due to the steric inhibition, by the gem-dimethyl group, of reaction at N-4 in compound **100**. It must be noted however that both the 1,7- and 1,4-bases appear to quaternize with equal ease and also that the Brooker deviations in the cyanine dyes containing the 1,4-diaza ring show that N-1 in that ring is more basic than either of the nitrogens in the 1,7-diaza analog. Hence, an electronic influence may be the controlling factor.

Quaternary salt formation by the 1,5-diaza-3*H*-indene **103** is reported to take place only at N-5¹⁵⁹ to give **104**. This information is



from a patent specification and therefore further details are not available. The formation of this salt is not surprising in view of the behavior of the other isomers.

2. Oxazolopyridines

Of the four possible oxazolopyridines, two have been studied with respect to quaternization reactions. Frazer and Tittensor¹⁶⁰ prepared 2-alkyl- and 2-aryl-oxazolo[4,5-*c*]pyridines (**105**; Y = H) and converted them into methiodides, the structures of which have not been determined. Subsequently Takahashi *et al.* prepared the corresponding 5-methyl (**105**; Y = Me)¹⁶¹ and 2-methyl-5-nitro compounds¹⁶² and

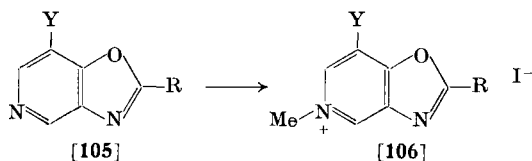
¹⁵⁹ G. E. Ficken and J. D. Kendall, British Patent 841,588 (1960).

¹⁶⁰ J. Frazer and E. Tittensor, *J. Chem. Soc.* 1781 (1956).

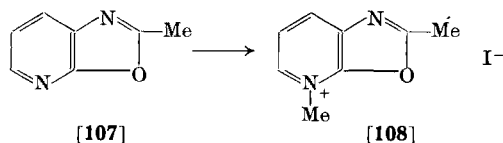
¹⁶¹ T. Takahashi and A. Koshiro, *Yakugaku Zasshi*, **79**, 291 (1959); *Chem. Abstr.* **53**, 15076 (1959).

¹⁶² T. Takahashi and A. Koshiro, *Chem. Pharm. Bull. (Tokyo)* **9**, 426 (1961); *Chem. Abstr.* **55**, 27310 (1961).

their methiodides. The nitro-methiodide decomposed quickly in boiling methanol to give 3-acetamido-1-methyl-5-nitro-4-pyridone, which proved that quaternization had taken place on the pyridine-nitrogen to give the salt **106** ($R = \text{Me}$, $Y = \text{NO}_2$).



The corresponding [5,4-*b*]-compound (**107**) was prepared similarly and treated with methyl iodide¹⁶³ to give a quaternary salt which was shown¹⁶¹ to have structure **108**, because mild alkaline hydrolysis gave 3-acetamido-1-methyl-2-pyridone. Again, quaternization took place on the pyridine-nitrogen, which is different from the behavior of the corresponding 1,4-diazaindene mentioned above.



3. Thiazolopyridines

Work on the thiazolopyridines has been centered on the 2-methyl derivatives and their conversion into cyanine dyes. Takahashi *et al.* prepared a number of substituted thiazolo[5,4-*b*]pyridines (**109**; $Y = \text{MeO}$,¹⁶⁴ EtO , Cl ,¹⁶⁵ and Et_2N ¹⁶⁶), all of which form methiodides (**110**) as evidenced by the high reactivity of the 2-methyl group. A parallel will be seen between these compounds and the 1,4-diaza-3*H*-indenes. Kiprianov reports⁴⁵ the interesting observation that the etho-toluene-*p*-sulfonate of **109** ($Y = \text{H}$) does not contain a reactive methyl group; presumably when Y is H the steric and electronic

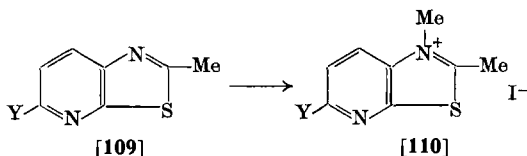
¹⁶³ A. Koshiro, *Chem. Pharm. Bull. (Tokyo)* **7**, 725 (1959); *Chem. Abstr.* **55**, 23493 (1961).

¹⁶⁴ Y. Yamamoto and T. Takahashi, *J. Pharm. Soc. Japan* **71**, 1436 (1951); *Chem. Abstr.* **46**, 8110 (1952).

¹⁶⁵ T. Takahashi and K. Sato, *J. Pharm. Soc. Japan* **76**, 195 (1956); *Chem. Abstr.* **50**, 13915 (1956).

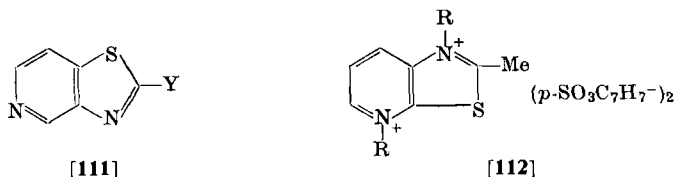
¹⁶⁶ T. Takahashi and K. Satake, *J. Pharm. Soc. Japan* **72**, 463 (1952); *Chem. Abstr.* **47**, 6405 (1953).

effects of group Y are not dominant and quaternization takes place on the pyridine-nitrogen atom. However, the Russian workers report that under vigorous conditions bis-metho- and -etho-salts (**112**) are



formed from **109** (Y = H), and these salts possess a reactive methyl group.⁴⁵ The formation of two quaternary centers in such proximity is unusual.

The quaternary salt from 2-methylthiothiazolo[4,5-*c*]pyridine (**111**; Y = SMe) has been described but no structure has been advanced.¹⁶⁷ Again the Russian workers report that a bis-etho-toluene-*p*-sulfonate



of **111** (Y = Me) contains a reactive methyl group, and it seems quite likely that quaternization on the pyridine-nitrogen is aided in the methylthio compound (**111**; Y = SMe) by the influence of the substituent.⁴⁵

B. TETRAZAINDENES

1. Purines

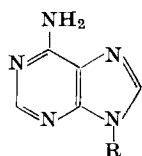
There has been considerable interest recently in the quaternization of purine compounds, although most of those examined have contained hydroxyl or amino substituents and therefore products may be regarded as the acid salts of N-alkylated derivatives.

The action of methyl toluene-*p*-sulfonate on adenine (**113**; R = H) is reported to give the 3-methyl derivative (**114**),¹⁶⁸ while the action

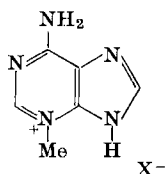
¹⁶⁷ T. Takahashi, K. Ueda, and T. Ichimoto, *Pharm. Bull. (Japan)* **3**, 356 (1955); *Chem. Abstr.* **50**, 16770 (1956).

¹⁶⁸ J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.* **84**, 1962 (1962).

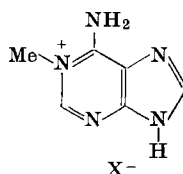
of dimethyl sulfate in dimethylformamide on adenosine (**113**; R = d-ribose), followed by acid hydrolysis, gave 31% of 1-methyladenine (**115**) and small amounts of the 3-methyl (**114**) and 1,3-dimethyl derivatives (**116**), all as their sulfates.¹⁶⁹ Inosine behaves similarly to



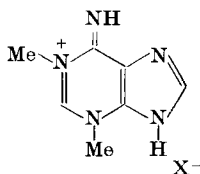
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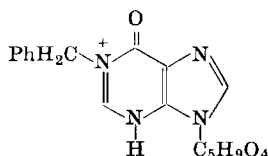
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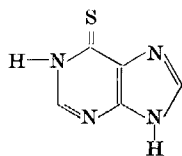


[116]

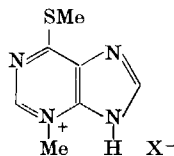


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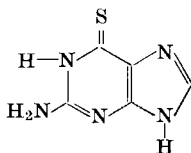
adenosine and with benzyl chloride gave **117**.¹⁷⁰ As would be expected, purine-6-thiol (**118**) undergoes methylation first on the sulfur atom when treated with methyl toluene-*p*-sulfonate and then quaternizes on N-3 to give **119**, but, surprisingly, 2-aminopurine-6-thiol (**120**)



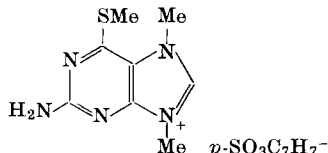
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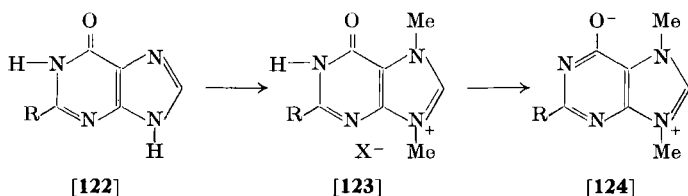
[121]

¹⁶⁹ P. Brookes and P. D. Lawley, *J. Chem. Soc.* 539 (1960).

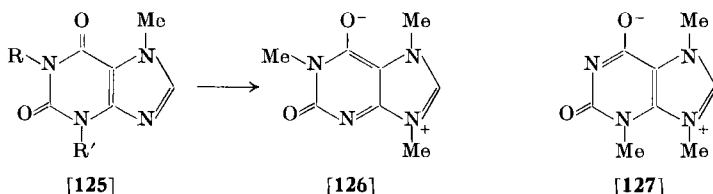
¹⁷⁰ E. Shaw, *Intern. Congr. Pure Appl. Chem.*, 16th, Paris, 1957, Vol. 2, 276 (1957).

reacts with the same quaternizing reagent in dimethylacetamide to give the 7,9-dimethyl derivative (**121**) by attack on the imidazole ring.¹⁶⁸ The same salt (**121**) is also formed by 2-amino-7-methylpurine-2-thiol, 2-amino-9-methylpurine-2-thiol, and 2-amino-9-methyl-6-methylthio- and 2-amino-6-methylthio-purine thus establishing the correctness of its structure. This salt shows no tendency to lose toluenesulfonic acid easily.¹⁶⁸

All the 6-hoxypurines so far investigated react with quaternizing reagents in the imidazole ring to give 7,9-dimethyl derivatives which are easily converted by ammonia or alkali into betaines. Thus, guanine (**122**; R = NH₂) and 7- and 9-methylguanine^{171, 172} give, by the action of methyl toluene-*p*-sulfonate, the salt **123** (R = NH₂) and then the betaine **124** (R = NH₂). Similarly, 6-hoxypurine-2-thiol



(**122**; R = SH) gives the betaine **124** (R = SMe), xanthine¹⁶⁸ (**122**; R = HO) and 9-methylxanthine^{173, 174} yield the betaine **124** (R = HO), and hypoxanthine (**122**, R = H) gives the betaine **124** (R = H).¹⁶⁸ In the same way, the reaction of methyl toluene-*p*-sulfonate and 1,9-dimethylxanthine (**125**; R = Me, R' = H) gives the betaine **126**, and 3,9-dimethylxanthine (**125**; R = H, R' = Me) gives the corresponding 3-methylbetaine (**127**); both of these betaines are formed *via* the quaternary salts.¹⁷³



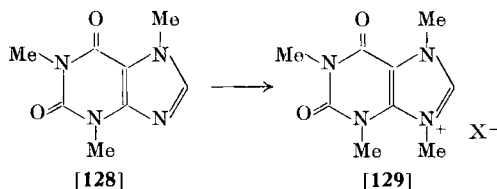
¹⁷¹ H. Bredereck, O. Christmann, and W. Koser, *Chem. Ber.* **93**, 1206 (1960).

¹⁷² W. Pfeiderer, *Ann. Chem.* **647**, 167 (1962).

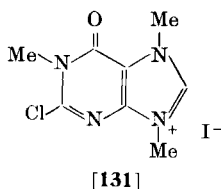
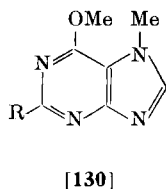
¹⁷³ W. Pfeiderer, *Ann. Chem.* **647**, 161 (1962).

¹⁷⁴ H. Bredereck, G. Kupsch, and H. Wieland, *Chem. Ber.* **92**, 566 (1959).

Caffeine (**128**) and dimethyl sulfate in nitrobenzene give the fully methylated dioxo compound **129**.¹⁷⁴ In the same way that 2,4-dialkoxypyrimidines give unstable quaternary salts which decompose to the N-alkyl oxo compounds even at room temperature, the action of



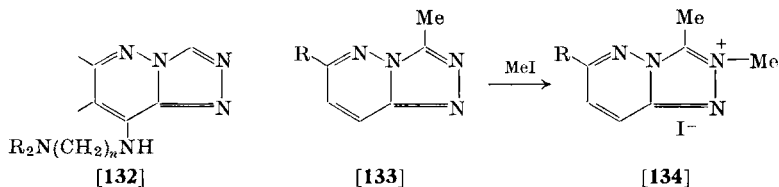
methyl iodide on 2,6-dimethoxy-7-methylpurine (**130**; R = OMe) gives caffeine (**128**), which is also obtained by heating the same base, i.e. **130** (R = OMe), without the quaternizing reagent.¹⁷⁵ However, the 2-chloro compound **130** (R = Cl), which is quite stable to heat, gives, on heating with methyl iodide, a methiodide of 2-chloro-1,7-dimethylxanthine,¹⁷⁵ which, on the basis of more recent work quoted above, is probably the 9-methiodide (**131**).



2. Triazaindolizines

Quaternary salts have been prepared from a number of these bases.

7-(Dialkylaminoalkyl)amino-1,2,3a,4-tetraazaindenes (**132**) were prepared and converted into mono-quaternary salts, but no structures were assigned to the salts and the quaternary center may well be in the side-chain.¹⁷⁶ When this ring system carries 3-methyl and 5-alkyl or

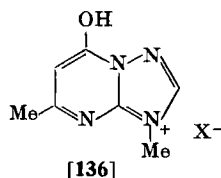
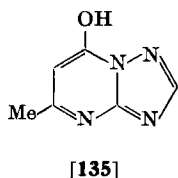


¹⁷⁵ E. Bergmann and H. Heimhold, *J. Chem. Soc.* 955 (1935).

¹⁷⁶ E. A. Steck and R. P. Brundage, *J. Am. Chem. Soc.* **81**, 6289 (1959).

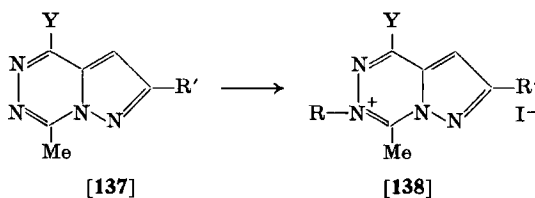
-aryl substituents (**133**) it quaternizes readily to give the N-2 salts (**134**) as shown by the reactivity of the 3-methyl group.¹⁷⁷

Fusion of methyl or ethyl toluene-*p*-sulfonates with 4-hydroxy-6-methyl-1,3,3a,7-tetraazaindene (**135**) gives only one salt, which on treatment with alkali is converted into a N-alkyl-4-oxo derivative.



The latter compound is not the 7-alkyl derivative, and the salt is believed to be **136**¹⁷⁸ by analogy with the quaternization behavior of 1,2,4-triazoles.¹⁷⁹

3,3a,5,6-Tetraazaindenes with 4-methyl, 7-alkoxy or -alkylthio, and 2-alkyl or -aryl substituents (**137**) have been prepared, and all these bases undergo ready quaternization with methyl or ethyl iodides in benzene to give the 5-salts (**138**).¹⁸⁰ This ring system therefore



behaves like a substituted pyridazine, the position of quaternization being controlled by the 4- and 7-substituents.

C. NAPHTHYRIDINES

A number of naphthyridines have been converted into their quaternary salts, but no systematic study has been reported.

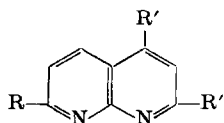
¹⁷⁷ G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, British Patent 839,020 (1960).

¹⁷⁸ V. C. Chambers, *J. Am. Chem. Soc.* **82**, 605 (1960).

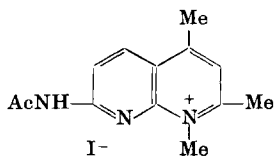
¹⁷⁹ G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind. (London)* 1458 (1954).

¹⁸⁰ G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, British Patent 862,825 (1961).

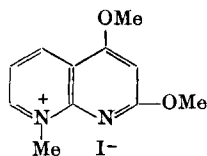
Treatment of 7-acetamido-2,4-dimethyl-1,8-naphthyridine (**139**; R = NHAc, R' = Me) with ethyl iodide at 110° for 24 hr gave an ethiodide; the corresponding 4-phenyl compound and methyl iodide formed a methiodide. Both of these salts possess a reactive methyl group and are therefore the 1-salts (cf. **140**).¹⁸¹ The easily formed



[139]



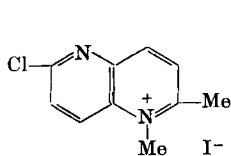
[140]



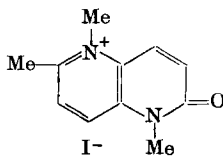
[141]

methiodide of 2,4-dimethoxy-1,8-naphthyridine was shown, by its oxidation with potassium ferricyanide to the corresponding oxo-dimethoxy compound, to be the 8-salt (**141**).¹⁸²

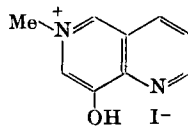
A methiodide of 6-chloro-2-methyl-1,5-naphthyridine has been prepared¹⁸³; no structure was assigned, but it is probably the 1-salt (**142**). The 5-N atom of 1,6-dimethyl-2-naphthyridone undergoes



[142]



[143]



[144]

quaternization on treating the base with methyl iodide giving the salt **143**¹⁸⁴; reaction does not occur at the oxo group. Methyl iodide reacts easily with 8-hydroxy-1,6-naphthyridine at N-6,¹²⁵ and the position of quaternization is proved by the fact that **144** still forms a nickel complex; presumably the 8-hydroxyl group shields the N-1 atom from attack.

D. PHENANTHROLINES

It has been found that treatment of *m*- or 1,7-phenanthroline (**145**; R = R' = H) with dimethyl sulfate for 1 hr at 100° gives the 7-salt

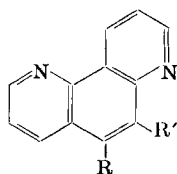
¹⁸¹ M. Pailer and E. Kuhn, *Monatsh. Chem.* **84**, 85 (1953).

¹⁸² G. Köller and E. Kandler, *Monatsh. Chem.* **58**, 213 (1931).

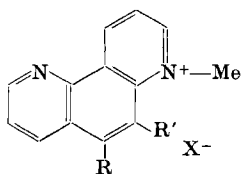
¹⁸³ T. Takahashi, T. Yatsuka, and S. Senda, *J. Pharm. Soc. Japan* **64**, No. 7/8A, 9 (1944); *Chem. Abstr.* **46**, 110 (1952).

¹⁸⁴ V. Petrow and B. Sturgeon, *J. Chem. Soc.* 1157 (1949).

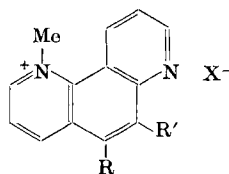
(**146**; $R = R' = H$).¹⁸⁵ Presumably, the shielding of N-1 hinders reaction at that site. This supposition is supported by the finding that 5-acetamido-1,7-phenanthroline (**145**; $R = NHAc$, $R' = H$) reacts readily with methyl iodide to give a salt believed to have structure **146** ($R = NHAc$, $R' = H$) whereas the 6-acetamido compound (**146**; $R = H$, $R' = NHAc$) will not quaternize with methyl iodide. However,



[145]



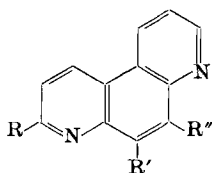
[146]



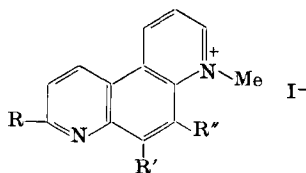
[147]

146 ($R = H$, $R' = NHAc$) reacts with methyl toluene-*p*-sulfonate at 120°–130° to yield a quaternary salt which is thought to be **147** ($R = H$, $R' = NHAc$); reaction is believed to occur at N-1 in spite of the proximity of the hydrogen atom in the 10-position.¹⁸⁶

Sykes¹⁸⁷ has studied a number of substituted 4,7-phenanthrolines (**148**). Since the ring system is symmetrical, as is also the case with the 1,10-compound, the position of quaternization is controlled by the substituents. In the first paper, 5-acetamido, -bromo, and -chloro



[148]



[149]

derivatives (**148**; $R = R' = H$, $R' = NHAc$, Br, or Cl) were reported to react with methyl iodide at 100° during 30 min to give, in all cases, the 7-salts (**149**; $R = R' = H$, $R' = NHAc$, Br, or Cl). The structures of the salts were proved by unambiguous synthesis of the isomeric 5-chloro-4-salt (**149**; $R = R' = H$, $R' = Cl$) from the metho-toluene-*p*-sulfonate of 6-acetamido-8-chloroquinoline.⁶² The second series of compounds

¹⁸⁵ W. O. Kermack and W. Webster, *J. Chem. Soc.* 213 (1942).

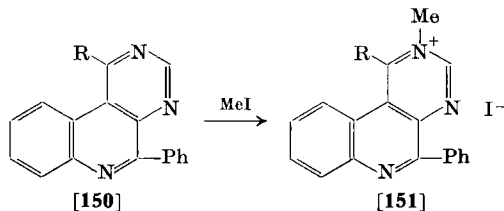
¹⁸⁶ R. D. Haworth and W. O. Sykes, *J. Chem. Soc.* 311 (1944).

¹⁸⁷ W. O. Sykes, *J. Chem. Soc.* 3087 (1956).

shielded included the 3-chloro, -methoxy, -methyl, -carboxy, and -ethoxycarbonyl derivatives of **149** ($R' = R'' = H$), and in all cases salt formation occurred at N-7.¹⁸⁷ The ease of quaternization varied with the nature of the 3-substituent, being easiest with the 3-methyl compound and most difficult with the 3-carboxy derivative; the other derivatives were of intermediate reactivity. Although the electronic effects of the 3-substituents affect the rate of quaternization, the steric influence of these substituents must cause that reaction always to occur at N-7. The structure assignment of the 3,7-dimethyl salt (**149**; $R' = R'' = H$, $R = Me$) rests on the fact that can be oxidized to the 3,7-dimethyl-8-oxo derivative, which was also obtained (in low yield) from 6-amino-1-methyl-2-quinolone by a Skraup reaction.

E. TRIAZAPHENANTHRENES

Two triazaphenanthrenes have been studied recently by Atkinson and Mattocks.¹⁸⁸ 10-Phenyl- (**150**; $R = H$) and 10-phenyl-4-amino-1,3,9-triazaphenanthrene (**150**; $R = NH_2$) were both shown to quaternize at N-3. The methiodide (**151**; $R = NH_2$) of the amino compound



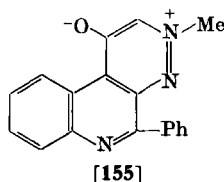
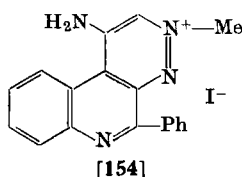
was easily converted by alkali into its 4-imino-2-methyl derivative which then underwent acid hydrolysis to give 2-methyl-4-oxo-10-phenyl-1,3,9-triazaphenanthrene (**152**). The latter compound, when heated with soda lime, gave methylamine and 3-amino-2-phenylquinoline, which is also obtained from the original methiodide (**151**;



¹⁸⁸ C. M. Atkinson and A. R. Mattocks, *J. Chem. Soc.* 1671 (1962).

R = NH₂) by the same treatment. The salt **151** (R = H) also gave methylamine and 3-amino-2-phenylquinoline when heated with soda lime.

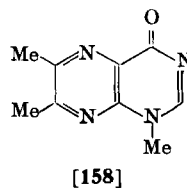
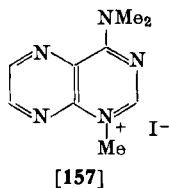
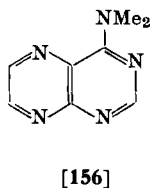
The position of quaternization in the isomeric ring system, 1,2,9-triazaphenanthrene, was not settled so clearly. The methiodide of 4-amino-10-phenyl-1,2,9-triazaphenanthrene (**153**) is converted by the action of alkali into a labile compound, which regenerates the quaternary salt on treatment with hydriodic acid. The labile compound gave 3-amino-2-phenylquinoline on heating with soda lime.



On boiling the methiodide with 70% sulfuric acid an N-methyl-oxo derivative was obtained, and this in turn gave 3-amino-2-phenylquinoline, methylamine, and ammonia on fusion with soda lime. The bulk of the evidence therefore favors quaternization at N-2 (cf. **154**), in which case the acid-hydrolysis product is **155**. Quaternization at N-2 would be expected because of the steric influence of the 10-phenyl group and the influence of the 4-amino group (cf. 4-hydroxypyridazine⁹⁰) in the pyridazine-type ring, although the partial double-bond character of that ring is probably different from that in pyridazine itself.

F. PTERIDINES

It is only recently that the first pteridine quaternary salt was prepared. Brown and Jacobson treated 4-dimethylaminopteridine (**156**) and its 6,7-dimethyl derivative with methyl iodide in boiling methanol and obtained the corresponding salts (cf. **157**).¹⁸⁹ The structure of these



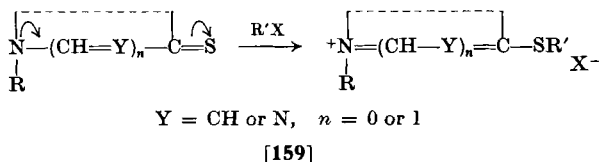
¹⁸⁹ D. J. Brown and N. W. Jacobson, *J. Chem. Soc.* 1978 (1960).

salts was ascertained by mild alkaline hydrolysis of the 6,7-dimethyl compound to the 1-methyl-4-pteridone **158**.

VI. Reaction at Atoms Other Than Nitrogen

A. SULFUR

The mesomeric effect of the C=S linkage is very pronounced and is responsible for the facile quaternization of heterocyclic N-alkylated thiones (**159**); this effect is operative even when such a shift does not increase the aromaticity of the ring. Thione derivatives of pyridazine,⁸⁶ benzothiazole,¹⁹⁰ quinazoline,⁵¹ 1,3-thiazine,¹⁹¹ triazole,⁸² and isoindole¹⁹² are examples of compounds which readily form quaternary salts.



The ease with which this reaction proceeds and its reversibility are responsible for some apparent anomalies. Ethyl iodide and 2-methylthiobenzothiazole were found to give 2-ethylthiobenzothiazole methiodide in addition to the expected 2-methylthioethiodide,¹⁹³ whereas similar quinoline¹⁹⁴ and 1,3-thiazine compounds¹⁹⁵ were reported to give only the transposed product. Fry and Kendall studied the reactions of the benzothiazole derivatives and found that the reaction proceeds *via* alkylation on the nitrogen, followed by formation of the thiones, which then give salts by addition¹⁹⁰; a series of such changes could give rise to all the products actually isolated. Further, reactions of methyl or ethyl iodides or toluene-*p*-sulfonates with benzothiazole derivatives yielded mixtures of products.

Another type of thione in which quaternization occurs readily is that possessing a dipolar, or meso-ionic, structure. Two examples have been reported recently. The ring-closed product obtained from the

¹⁹⁰ D. J. Fry and J. D. Kendall, *J. Chem. Soc.* 1716 (1951).

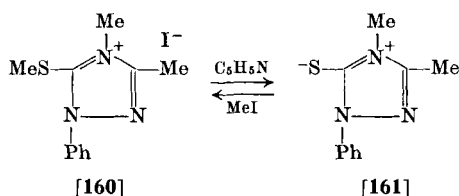
¹⁹¹ B. Beilenson, F. M. Hamer, and R. J. Rathbone, *J. Chem. Soc.* 222 (1945).

¹⁹² G. E. Ficken and J. D. Kendall, *J. Chem. Soc.* 1537 (1960).

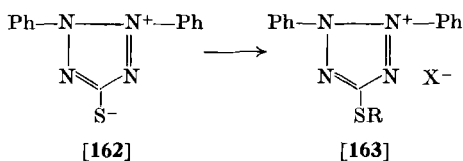
¹⁹³ W. A. Sexton, *J. Chem. Soc.* 470 (1939).

¹⁹⁴ B. Beilenson and F. M. Hamer, *J. Chem. Soc.* 148 (1939).

¹⁹⁵ F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.* 243 (1943).

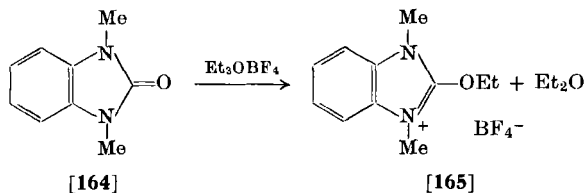


reaction of 4-methyl-1-phenylthiosemicarbazide with acetic anhydride reacts readily with methyl iodide to give the triazole salt **160**; the base, which is readily regenerated by boiling the salt with pyridine, must therefore be the dipolar compound **161**.⁸² In the same way, Ogilvie and Corwin found that the oxidation product of dithizone, the tetrazolium dipolar compound **162**, will react with methyl iodide or chloroacetic acid to give **163** (R = Me or CH₂CO₂H), which shows all the usual reactions of a tetrazolium salt.¹⁹⁶



B. OXYGEN

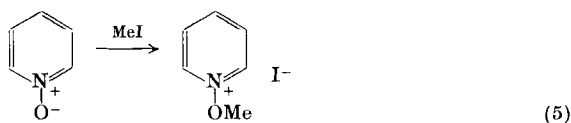
The formation of quaternary salts by attack at an oxygen atom is only achievable in certain special cases. Most of the attempts to effect reactions of this type with N-alkyl- α -oxo derivatives have failed. Until recently it might have been assumed that 2-alkoxy-quaternary salts were unobtainable, the usual product from reactions with the alkoxy derivatives being the N-alkyl-oxo compounds (see Section IV,C). Recently, however, Meerwein and his co-workers found that triethyloxonium borofluoride and a number of N-methyl- α -oxo



¹⁹⁶ J. W. Ogilvie and A. H. Corwin, *J. Am. Chem. Soc.* **83**, 5023 (1961).

compounds undergo a reaction similar to that which occurs readily with the thiones.¹⁹⁷ Thus, 1,3-dimethyl-2-benzimidazolone (**164**) gives the salt **165**, which is stable up to its melting point (152°). Similar compounds are formed by 1-methyl-2-quinolone, 3-methyl-2-benzoxazolone, and 3-methyl-2-benzothiazolone, although the last mentioned is unstable in moist air.

The other known case, a more general one, of attack at an oxygen atom is the formation of N-alkoxy-quaternary salts by quaternization of the N-oxides¹⁹⁸ and is illustrated by Eq. (5).



C. CARBON

Nucleophilic attack at a carbon atom, followed by a mesomeric shift to make a nitrogen atom quaternary, has been known for many years. The best example is the formation of 1,3,3-trisubstituted 3*H*-indole salts by the action of alkyl halides on 1,3-disubstituted indoles.

An interesting example of a reaction of this type was provided more recently by Robinson and Saxton¹⁹⁹ who found that methyl iodide and **166** (R = Et) gives the same salt as is obtained from the interaction of **166** (R = Me) and ethyl iodide. The structure of the salt must therefore be **167**, the process being a typical indole-type reaction.



VII. The Mechanism of Quaternization

The quaternization reaction has been found^{1, 2, 50, 200} to be a bi-molecular reaction which is first order with respect to both reactants

¹⁹⁷ H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann. Chem.* **641**, 1 (1961).

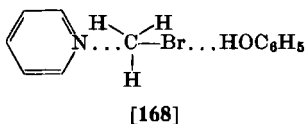
¹⁹⁸ E. Ochiai, *J. Org. Chem.* **18**, 534 (1953).

¹⁹⁹ R. Robinson and J. E. Saxton, *J. Chem. Soc.* 976 (1952).

²⁰⁰ C. N. Hinshelwood and K. J. Laidler, *J. Chem. Soc.* 858 (1938).

and is usually regarded as a pure S_N2 process. Bunton *et al.*, as part of a series of nucleophilic studies, found that the reaction of pyridine with methyl iodide in sulfur dioxide was bimolecular while the interaction of *t*-butyl bromide and pyridine to give isobutylene was unimolecular.³ The reaction of pyridine and *n*-butyl bromide also showed second-order kinetics in tetramethylene sulfone,⁴⁹ dimethylsulfolane,⁵⁴ and propylene carbonate.²⁰¹ A wide range of bromo compounds, with α -carbonyl groups, including ethyl α -bromoacetate and phenacyl bromide, also undergo bimolecular reactions with pyridine in methanol.³⁰ Pearson and co-workers³⁰ noted that bromo compounds with an α -carbonyl group are more reactive as quaternizing reagents than are the corresponding nitro or sulfo derivatives. This fact and the observations that 2,4,6-trimethylphenacyl bromide reacts slower than phenacyl bromide itself (see Table I) are attributed to steric hindrance and are considered to support backside attack as the mechanism of quaternization.

Swain and Eddy have queried the wide applicability of the S_N1 and S_N2 mechanisms and favored a push-pull termolecular process for the reaction of pyridine with methyl bromide in benzene solution; for example, they have suggested that the effects observed on the addition of methanol, phenol, *p*-nitrophenol, and mercuric bromide to the reaction mixture can be explained by an intermediate of type **168**.²⁰²



These substances accelerate the reaction, and their effectiveness increases in the order given. This suggestion was questioned by Pocker, who found that the effects of such added substances were not directly proportional to their concentrations and could easily be explained by macro effects on the solvent character.²⁰³ He also found that common-ion effects were small in the reaction, the effect of added 1-methylpyridinium bromide was negligible, and that there was no evidence for surface catalysis on the walls of the vessel. There is an exact parallel between the relative rates of the Finkelstein reactions

²⁰¹ P. L. Kronick and R. M. Fuoss, *J. Am. Chem. Soc.* **77**, 6115 (1955).

²⁰² C. G. Swain and R. W. Eddy, *J. Am. Chem. Soc.* **70**, 2989 (1948).

²⁰³ Y. Pocker, *J. Chem. Soc.* 1279 (1957).

for various alkyl bromides and those of quaternization,²⁰⁴ and therefore Pocker²⁰³ concluded that the quaternizing process was a true S_N2 reaction.

The isotope effect, using C^{14} -labeled methyl iodide, in the quaternization of pyridine in benzene solution has been investigated by Bender and Hoeg.²⁰⁵ The isotope effect, 1.4, was slightly higher than the values obtained for similar reactions with triethylamine, hydroxyl ion, and silver ion, which were 1.10, 1.09, and 1.09, respectively. The magnitude is consistent with the suggestion that the reaction proceeds only with bond rupture, which again would provide support for the S_N2 three-center transition state. The higher value obtained with pyridine is probably due to the fact that the activation energy is also the highest of the four reactions.

Cavell and Chapman³¹ made the interesting observation that a difference exists between the orbital involved in the quaternization of aromatic nitrogen heterocycles and aromatic amines, which appears not to have been considered by later workers. The lone pair which exists in an sp^2 orbital of the aniline nitrogen must conjugate, as shown by so many properties, with the aromatic ring and on protonation or quaternization sp^3 hybridization occurs with a presumed loss of mesomerism, whereas in pyridine the nitrogen atom remains sp^2 hybridized in the base whether it is protonated or quaternized. Similarly, in a saturated compound, the nitrogen atom is sp^3 hybridized in the base and salt forms.

The influence of solvent polarity on the rate of quaternization is well known and recent measurements have supported the general view that the more polar solvents produce a faster reaction.¹ Fuoss and his colleagues determined the rate of reaction in a number of solvents^{49, 54, 201} and discovered that the process was twice as fast in tetramethylene sulfone as in propylene carbonate, even though the dielectric constants of these solvents are 42 and 65, respectively. In another study a mixture of diphenyl ether with propylene carbonate and ethylene carbonate was used to cover the range of dielectric constants from 3.6 to 65.²⁰⁶ The reactions showed second-order kinetics up to 90% completion except for pure diphenyl ether where the rate decreased with time and was truly second order only up to 10%. It was found that solvent mixtures containing more than 50% propylene

²⁰⁴ C. N. Hinshelwood and C. A. Winkler, *J. Chem. Soc.* 1147 (1935).

²⁰⁵ M. L. Bender and D. F. Hoeg, *J. Am. Chem. Soc.* **79**, 5649 (1957).

²⁰⁶ M. Watanabe and R. M. Fuoss, *J. Am. Chem. Soc.* **78**, 527 (1956).

carbonate gave a higher rate than expected, which up to that proportion increased linearly with the dielectric constant. This fact and the facilitating effect of both ethylene and propylene carbonates compared with the sulfones^{54, 201} suggest that short-range effects are operating which may almost have a specificity in them, and all the evidence points to a partially ionized transition state. It is also of interest to observe that although the reaction rate is lowest in diphenyl ether, this solvent also has the lowest activation energy and that it is the low value of the statistical factor in the rate equation which is responsible for its slowness.

In conclusion, it may be stated that the classic S_N2 process is still the best picture, although the solvent clearly plays an important part.

Note Added in Proof

Recent work has justified the suspicions that the methylated cinnolones had been allocated the incorrect structures. D. E. Ames and H. Z. Kucharska [*J. Chem. Soc.* 4924 (1963)] have shown that the compound previously believed to be 1-methyl-4-cinnolone is the dipolar anhydro-base of 4-hydroxy-2-methyl-cinnolinium hydroxide. It is likely, therefore, that those cinnoline salts whose structures had been based upon the presumed 1-methyl-4-cinnolones are, in fact, 2-salts of structure **56**. (Cf. p. 28.)

The Reactions of Heterocyclic Compounds with Carbenes

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I. Introduction

A. SCOPE OF REVIEW

In this review an attempt is made to discuss all the important interactions of highly reactive divalent carbon derivatives (carbenes, methylenes) and heterocyclic compounds and the accompanying molecular rearrangements. The most widely studied reactions have been those of dihalocarbenes, particularly dichlorocarbene, and the α -ketocarbenes obtained by photolytic or copper-catalyzed decomposition of diazo compounds such as diazoacetic ester or diazoacetone. The reactions of diazomethane with heterocyclic compounds have already been reviewed in this series.¹

In spite of long and continued interest in the reactions to be described, there has been relatively little work on the reaction

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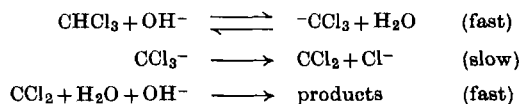
¹ R. Gompper, in "Advances in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. II, p. 245. Academic Press, New York, 1963.

mechanisms, and even less quantitative work, and much remains to be done in this direction.

B. HISTORICAL

The idea that dichlorocarbene is an intermediate in the basic hydrolysis of chloroform is now one hundred years old. It was first suggested by Geuther² in 1862 to explain the formation of carbon monoxide, in addition to formate ions, in the reaction of chloroform (and similarly, bromoform) with alkali. At the end of the last century Nef³ interpreted several well-known reactions involving chloroform and a base in terms of the intermediate formation of dichlorocarbene. These reactions included the ring expansion of pyrroles to pyridines⁴ and of indoles to quinolines,⁵ as well as the Hofmann carbylamine test for primary amines and the Reimer-Tiemann formylation of phenols.

During the next fifty years the interest in derivatives of divalent carbon was mainly confined to methylene (CH_2) and substituted methylenes obtained by decomposition of the corresponding diazo compounds; this phase has been fully reviewed by Huisgen.⁶ The first convincing evidence for the formation of dichlorocarbene from chloroform was presented by Hine⁷ in 1950. Kinetic studies of the basic hydrolysis of chloroform in aqueous dioxane led to the suggestion that the rate-determining step was loss of chloride ion from the trichloromethyl anion which is formed in a rapid pre-equilibrium with hydroxide ions:



Hine and co-workers⁸ have since shown this scheme to be general for a variety of fluorine-free haloforms, and more recent work by Robinson⁹ has led to an improved rate expression for the basic hydrolysis of

² A. Geuther, *Ann. Chem.* **123**, 121 (1862).

³ J. U. Nef, *Ann. Chem.* **298**, 366 (1897).

⁴ G. L. Ciamician and M. Dennstedt, *Ber.* **14**, 1153 (1881); **15**, 1172 (1882).

⁵ G. Magnanini, *Ber.* **20**, 2608 (1887); **21**, 1940 (1888).

⁶ R. Huisgen, *Angew. Chem.* **67**, 439 (1955).

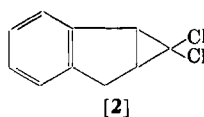
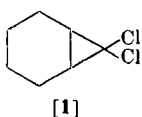
⁷ J. Hine, *J. Am. Chem. Soc.* **72**, 2438 (1950).

⁸ J. Hine, R. C. Peek, and B. D. Oakes, *J. Am. Chem. Soc.* **76**, 827 (1954); J. Hine and A. M. Dowell, *ibid.* **76**, 2688 (1954); J. Hine, A. M. Dowell, and J. E. Singley, *ibid.* **78**, 479 (1956).

⁹ E. A. Robinson, *J. Chem. Soc.* 1663 (1961).

chloroform and to suggested mechanisms for the formation of the products, carbon monoxide and formate ions.

Direct evidence for the existence of dichlorocarbene, by trapping with a suitable substrate, was obtained by Doering and Hoffmann in 1954.¹⁰ Dichlorocarbene was shown to add in a characteristic manner to the double bond of cyclohexene to give dichloronorcaradiene (**1**) in 59% yield; similar adducts were obtained with other olefins. Bromoform underwent an analogous reaction in the presence of olefins to give



the corresponding dibromocarbene adducts.¹⁰ These reactions were soon shown to involve stereospecific *cis* addition.¹¹ In 1955 Parham and Reiff¹² reported that the reaction of indenyl sodium and chloroform led to a ring-expanded product, 2-chloronaphthalene, and suggested that dichlorocarbene might be involved. They confirmed this in the following year by isolation of the adduct (**2**) from the reaction of indene, chloroform, and potassium *t*-butoxide in light petrol and subsequent conversion of the adduct into 2-chloronaphthalene.¹³ These observations have played an important part in much of the work to be described.

Carbene chemistry in general has been the subject of various reviews.¹⁴

C. REACTIVITY OF CARBENES

The neutral divalent carbon atom of a carbene, CX_2 , with its six valency electrons is electron deficient and hence electrophilic. The

¹⁰ W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.* **76**, 6162 (1954).

¹¹ P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.* **78**, 3409, 5430 (1956); W. von E. Doering and P. La Flamme, *ibid.* **78**, 5447 (1956).

¹² W. E. Parham and H. E. Reiff, *J. Am. Chem. Soc.* **77**, 1177 (1955).

¹³ W. E. Parham, H. E. Reiff, and P. Swartzentruber, *J. Am. Chem. Soc.* **78**, 1437 (1956).

¹⁴ I. L. Knunyants, N. P. Gambaryan, and E. M. Rohlin, *Usp. Khim.* **27**, 1361 (1958); W. Kirmse, *Angew. Chem.* **72**, 537 (1959) and **74**, 161 (1961); J. Leitich, *Oesterr. Chemiker-Ztg.* **61**, 164 (1960); J. Hine, "Physical Organic Chemistry", 2nd Edn., McGraw-Hill, New York, 1962; P. Miginiac, *Bull. Soc. Chim. France* 2000 (1962); E. Chinoporos, *Chem. Rev.* **63**, 235 (1963).

two non-bonding electrons may occupy the same orbital, with their spins paired (singlet state), and to a first approximation the three occupied orbitals will have a planar trigonal configuration about the sp^2 hybridized carbon atom, with a vacant orthogonal p-orbital. This structure is analogous to a classical carbonium ion and will be stabilized by interaction between the vacant p-orbital and suitably orientated occupied orbitals on the group X. Alternatively, the two non-bonding electrons may occupy different orbitals and have unpaired spins (triplet state) to give a diradical.

These singlet and triplet state species exhibit the important differences in chemical behavior to be expected. The former species, with their analogy to carbonium ions, are powerful electrophiles and the relative rates of their reaction with a series of substrates increases with the availability of electrons at the reaction center; their addition reactions with olefins are stereospecific. Triplet state species are expected to show the characteristics of radicals; i.e., the relative rates of additions to olefins do not follow the same pattern as those of electrophilic species and the additions are not stereospecific.

The parent species, methylene (obtained by photolysis of diazomethane), in which stabilization of the vacant orbital is not possible, is extraordinarily reactive and shows no selectivity in its gas- and liquid-phase reactions with the carbon-hydrogen bonds in a variety of saturated and unsaturated hydrocarbons¹⁵; this reaction has been shown to involve direct insertion into the C—H bond.¹⁶ With olefins stereospecific *cis* addition to the double bond occurred suggesting a singlet state for methylene.^{11, 17} Recent evidence shows that methylene is generated initially in an excited singlet state but degenerates, by collision with inert molecules, to a linear triplet ground state; photosensitization of the decomposition of diazomethane by benzophenone led directly to triplet state methylene.¹⁸ Methods of generation of methylene which adds to double bonds without insertion into C—H

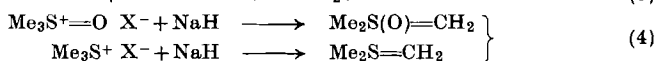
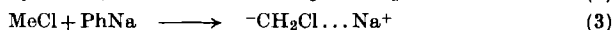
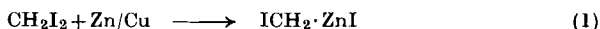
¹⁵ W. von E. Doering, R. G. Buttery, R. G. Laughlin, and N. Chaudhuri, *J. Am. Chem. Soc.* **78**, 3224 (1956).

¹⁶ W. von E. Doering and H. Prinzbach, *Tetrahedron* **6**, 24 (1959).

¹⁷ P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.* **78**, 4496, 6427 (1956); **79**, 6577 (1957); **81**, 3383 (1959).

¹⁸ F. A. L. Anet, R. F. W. Bader, and A.-M. van der Auwera, *J. Am. Chem. Soc.* **82**, 3217 (1960); H. M. Frey, *ibid.* **82**, 5947 (1960); B. S. Rabinovitch and D. W. Setser, *ibid.* **83**, 750 (1961); D. B. Richardson, M. C. Simmons, and I. D. Dvoretzky, *ibid.* **83**, 1934 (1961); K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *ibid.* **84**, 1015 (1962).

bonds, e.g. Eqs. (1-4),¹⁹⁻²² probably do not involve the free CH_2 species.



The electrophilic character of the dihalocarbenes, CCl_2 and CBr_2 , was established by their relative reactivities towards various nucleophiles⁸; they react stereospecifically with alkenes to give 1,1-dihalocyclopropanes as the only products.¹⁰ The relative rates of addition of these carbenes were found¹¹ to correlate well with other electrophilic, three-center additions, e.g. of Br^+ and HO^+ , but not with the addition of trichloromethyl radicals. The same pattern of reactivity is also shown in the additions of monochlorocarbene,²³ dimethylvinylidene carbene ($\text{Me}_2\text{C}=\text{C}=\text{C}$),²⁴ and ethoxycarbonyl carbene ($\text{CH} \cdot \text{CO}_2\text{Et}$).²⁵ In all cases the rate of addition increases with increasing alkyl substitution at the double bond. The expected gradation of reactivity in the chlorocarbenes is shown in their reactions with benzene. Methylene reacts by insertion into the $\text{C}-\text{H}$ bond, to give toluene, and by addition to the aromatic ring, followed by ring expansion, to give cycloheptatriene.²⁶ Monochlorocarbene gave only the product of ring expansion,²⁷ and dichlorocarbene did not react.²⁸

The reactions of carbenes, which are apparently unique in displaying electrophilic character in strongly basic solutions, include substitution, addition to multiple bonds, and co-ordination with lone pairs of electrons to form unstable ylides. This last reaction is of obvious relevance to a consideration of the reactions of heterocyclic compounds with carbenes and will be summarized.

The formation of hydrogen cyanide from ammonia by reaction with

¹⁹ H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.* **81**, 4256 (1959).

²⁰ V. Franzen and G. Wittig, *Angew. Chem.* **72**, 417 (1960).

²¹ L. Friedman and J. G. Berger, *J. Am. Chem. Soc.* **82**, 5758 (1960).

²² E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **84**, 867, 3782 (1962); V. Franzen and H.-E. Driessen, *Ber.* **96**, 1881 (1963).

²³ G. L. Closs and G. M. Schwartz, *J. Am. Chem. Soc.* **82**, 5729 (1960).

²⁴ H. D. Hartzler, *J. Am. Chem. Soc.* **83**, 4997 (1961).

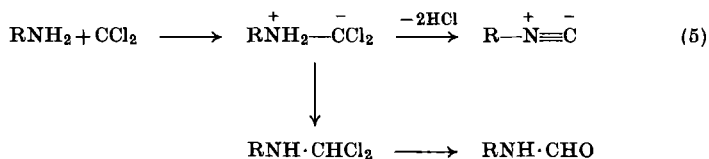
²⁵ P. S. Skell and R. M. Etter, *Chem. Ind. (London)* 624 (1958).

²⁶ W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **72**, 2305 (1950).

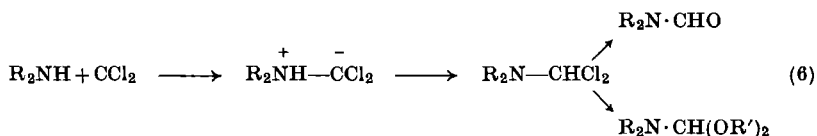
²⁷ G. L. Closs and L. E. Closs, *Tetrahedron Letters* **10**, 38 (1960).

²⁸ W. von E. Doering and W. A. Henderson, *J. Am. Chem. Soc.* **80**, 5274 (1958).

chloroform and alkali²⁹ and of diazomethane from hydrazine in a similar reaction³⁰ and the carbylamine reaction of primary amines presumably all involve initial reaction of dichlorocarbene with the basic nitrogen atom. In the last reaction Smith and Kalenda³¹ found formamides to be by-products, sometimes to the exclusion of the isocyanide, and proposed the mechanism shown in Eq. (5). Dichlorocarbene generated from sodium trichloroacetate in the presence of



primary amines similarly gave isocyanides.³² The reactions of this carbene with secondary^{33, 34} and tertiary amines³³ have also been reported. Secondary amines gave the corresponding formamides or



their acetals as in Eq. (6).³⁵ With tertiary amines the initially formed ylide underwent rearrangement or Hofmann elimination³³ [Eqs. (7) and (8)]. Halocarbenes also form ylides with the nucleophilic tervalent phosphorus atom^{36, 37}; the phosphoranes derived from tributylphosphine and triphenylphosphine have been used in the Wittig reaction with aldehydes and ketones to give the 1,1-dihaloethylenes, or the phosphoranes may be hydrolyzed *in situ*.³⁶

²⁹ C. R. Hauser, W. G. Kofron, W. R. Dunnivant, and W. F. Owens, *J. Org. Chem.* **26**, 2627 (1961).

³⁰ H. Staudinger and O. Kupfer, *Ber.* **45**, 505 (1912).

³¹ P. A. S. Smith and N. W. Kalenda, *J. Org. Chem.* **23**, 1599 (1958).

³² A. P. Krapcho, *J. Org. Chem.* **27**, 1089 (1962).

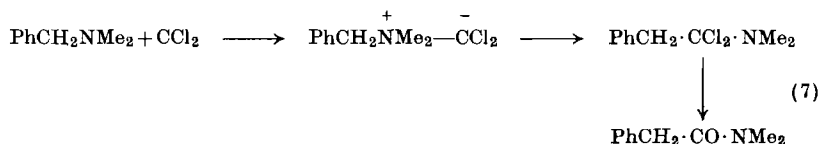
³³ M. Saunders and R. W. Murray, *Tetrahedron* **6**, 88 (1959); **11**, 1 (1960).

³⁴ M. B. Frankel, H. Feuer, and J. Bank, *Tetrahedron Letters* **7**, 5 (1959); A. Pierce and M. M. Joullie, *J. Org. Chem.* **27**, 2220 (1962).

³⁵ W. Stilz, unpublished results quoted in *Angew. Chem.* **72**, 838 (1960).

³⁶ A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.* **84**, 854 (1962).

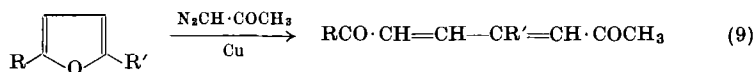
³⁷ D. S. Seyferth, S. O. Grim, and T. O. Read, *J. Am. Chem. Soc.* **83**, 1617 (1961); R. Oda, Y. Ito, and M. Okano, *Tetrahedron Letters* **1**, 7 (1964).



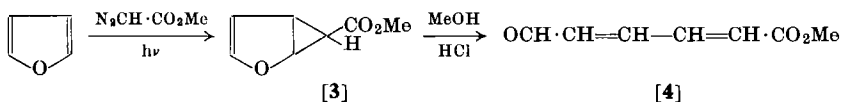
II. Reactions with Five-Membered Heterocyclic Rings

A. FURAN, THIOPHENE, AND THEIR BENZO-DERIVATIVES

With a few recent exceptions the reactions in this group have been with the α -ketocarbenes, $\text{CH}\cdot\text{COOMe}$, $\text{CH}\cdot\text{COOEt}$, and $\text{CH}\cdot\text{COCH}_3$, derived from the corresponding diazo compounds. Šorm and co-workers³⁸ have reported the ring-opening of furan and methylfurans upon reaction with diazoacetone decomposed by copper, *via* attack at



the less-substituted α -position [Eq. (9)]. Similarly 2-methylfuran and diazoacetic ester gave $\text{CH}_3\text{CO}\cdot\text{CH}=\text{CH}-\text{CH}=\text{CH}\cdot\text{CO}_2\text{Et}$. However, the photolytic decomposition of diazoacetic ester in furan gave the carbene adduct **3** which rearranged in methanolic hydrochloric acid to give the *trans,trans* muconaldehydic ester **4**.³⁹ Schenck and Steimetz



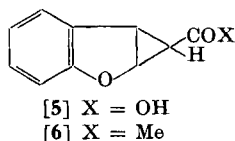
have extended these additions to methylfurans and dihydrofurans.³⁹ The photolytic or cuprous bromide catalyzed reactions of diazo-methane with furan and with thiophene gave the expected cyclopropane adducts, and no nuclear methylation.^{39a} In its reactions with diazoacetic ester and diazoacetone, benzofuran behaved, as in many

³⁸ J. Novák and F. Šorm, *Chem. Listy* **51**, 1693 (1957).

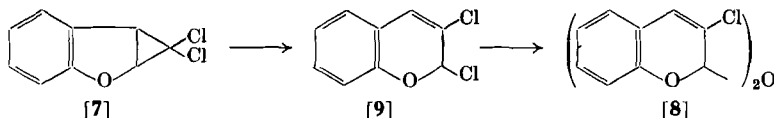
³⁹ G. O. Schenck and R. Steinmetz, *Angew. Chem.* **71**, 504 (1958); *Ann. Chem.* **668**, 19 (1963).

^{39a} E. Müller, H. Kessler, H. Fricke, and H. Suhr, *Tetrahedron Letters* **16**, 1047 (1963).

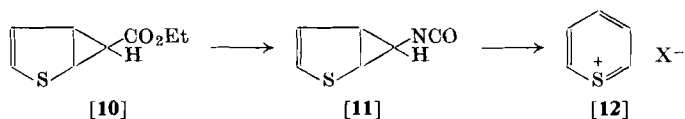
other reactions, as a vinyl ether to give (after hydrolysis) the cyclopropane acid **5** and ketone **6**, respectively.^{40, 41}



The only known reaction of a furan with a dihalocarbene is that recently reported between benzofuran and dichlorocarbene in hexane at 0°. ⁴² The initial adduct (**7**) could not be isolated but on hydrolysis gave the ring-expanded product **8**, possibly *via* **9**, in 15% yield. Benzothiophene was recovered in 92% yield under the same conditions. ⁴² 2,5-Dihydrofuran reacted with dichloro- and dibromocarbene to give the products of allylic insertion, 2-dihalogenomethyl-2,5-dihydrofuran, as well as the normal addition products. ^{42a}



Steinkopf and Augestad-Jensen ⁴³ in 1922 reported the reaction of diazoacetic ester with thiophene and the hydrolysis of the adduct (**10**) to an acid, m.p. 107°, of unknown identity. Pettit ^{43a} has used this adduct in the synthesis of the thiapyrylium cation (**10** → **11** → **12**). The same adduct (**10**) was obtained by photolysis of diazoacetic ester



⁴⁰ G. M. Badger, B. J. Christie, H. J. Rodda, and J. M. Pryke, *J. Chem. Soc.* 1179 (1958); G. M. Badger, H. J. Rodda, and J. M. Sasse, *ibid.* 4777 (1958).

⁴¹ J. Novák, J. Ratuský, V. Šneberg, and F. Šorm, *Chem. Listy* **51**, 479 (1957).

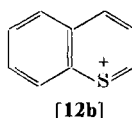
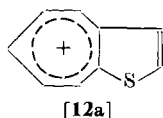
⁴² W. E. Parham, C. G. Fritz, R. W. Soeder, and R. M. Dodson, *J. Org. Chem.* **28**, 577 (1963).

^{42a} J. C. Anderson and C. B. Reese, *Chem. Ind. (London)* 575 (1963).

⁴³ W. Steinkopf and H. Augestad-Jensen, *Ann. Chem.* **428**, 154 (1922).

^{43a} R. Pettit, *Tetrahedron Letters* **23**, 11 (1960).

in thiophene; hydrolytic rearrangement with methanolic hydrochloric acid gave the 3-thienylacetic ester.³⁹ In contrast, the copper-catalyzed decomposition of diazoacetone with thiophene led directly to 2-thienylacetone.⁴¹ The reactions of diazoacetic ester with benzothiophene appear to be more complex than those with benzofuran; besides the expected addition to the heterocyclic ring, giving (after hydrolysis) the benzothiophene analog of **5**, there is evidence for addition to the benzene ring.⁴⁰ Furthermore, treatment of the crude reaction product from benzothiophene and diazoacetic ester in a manner analogous to **10** \rightarrow **11** \rightarrow **12** gave salts of the thienotropylium cation **12a**, derived from initial addition to the carbocyclic ring, rather than of the benzothiapyrylium cation **12b**.^{43b} The condensation



of certain benzothiophenes, under conditions resembling those of the Reimer-Tiemann reaction, to give photographic dyestuffs has been described in the patent literature.⁴⁴

There is plainly still much scope for systematic work on these reactions.

B. PYRROLES AND INDOLES

1. α -Ketocarbenes

The copper-catalyzed decomposition of diazoacetic ester in the presence of pyrrole was first described⁴⁵ in 1899 and later investigated in more detail by Nenitzescu and Solomonica.⁴⁶ Ethyl pyrrole-2-acetate (**13**), the normal product of electrophilic substitution, was obtained in 50% yield and was degraded to 2-methylpyrrole. Similarly *N*-methylpyrrole with two moles of diazoacetic ester gave, after hydrolysis, the 2,5-diacetic acid (**14**) while 2,3,5-trimethylpyrrole gave, after degradation, 2,3,4,5-tetramethylpyrrole by substitution of ethoxycarbonylcarbene at the less favored β -position. Nenitzescu and Solomonica also successfully treated pyrroles with phenyl-

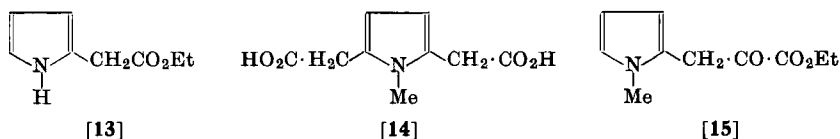
^{43b} D. Sullivan and R. Pettit, *Tetrahedron Letters* **6**, 401 (1963).

⁴⁴ I. G. Farbenindustrie A. G., British Patent 418,571 (1934).

⁴⁵ A. Piccinini, *Gazz. Chim. Ital.* **29**, 363 (1899).

⁴⁶ C. D. Nenitzescu and E. Solomonica, *Ber.* **64**, 1924 (1931).

benzoyldiazomethane and diazoacetoacetic ester. Diazopyruvic ester reacts similarly with *N*-methylpyrrole to give the 2-pyruvic ester (15).⁴⁷



Jackson and Manske⁴⁸ described the decomposition of diazoacetic ester with indoles to give, after hydrolysis, the 3-acetic acid and some 1,3-diacetic acid; no product of 2-substitution was found (see also ref. 49). Diazoacetone and diazopyruvic ester similarly gave the 3-substituted indoles.⁴⁷ Badger *et al.*⁴⁰ have also examined the reaction of *N*-methylindole, as well as of indole, with diazoacetic ester. Again only the 3-substituted product resulted and no evidence was obtained for addition.

2. Halocarbenes

The preceding reactions of pyrroles and indoles with oxygen-containing carbenes are unexceptional in that they furnish the expected products of electrophilic substitution. However, several long-established reactions of pyrroles and indoles involving their ring expansion to pyridines and quinolines, respectively, proceed under conditions now recognized as favorable to the formation of halocarbenes. These reactions have limited preparative value because of the low yields usually obtained but nevertheless have aroused much interest, particularly with regard to reaction mechanism (see, e.g., ref. 50).

Ciamician⁵¹ reported the formation of 3-halogenopyridines in low yield from the reaction of pyrrol potassium with chloroform, or bromoform, in ether. Similar reactions of pyrrole with benzal chloride and methylene iodide gave 3-phenylpyridine and traces of pyridine, respectively. These reactions were later reinvestigated by Alexander

⁴⁷ J. Ratuský and F. Šorm, *Chem. Listy* **51**, 1009 (1957).

⁴⁸ R. W. Jackson and R. H. F. Manske, *Can. J. Res.* **13B**, 170 (1935).

⁴⁹ S. S. Nametkin, N. N. Mel'nikov, and K. S. Bokarev, *Zhur. Priklad. Khim.* **29**, 459 (1956); *Chem. Abstr.* **50**, 13867 (1956).

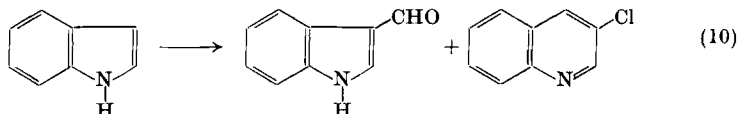
⁵⁰ H. Wynberg, *Chem. Rev.* **60**, 169 (1960).

⁵¹ G. L. Ciamician, *Ber.* **37**, 4201 (1904) and references cited therein.

*et al.*⁵² who confirmed the earlier work but could not improve the low yields, though several other bases were used.

Carbon tetrachloride was also found to react with pyrrol potassium to give 3-chloropyridine,⁴ however the mechanism is obscure and would justify further investigation.^{52a} In a preparatively useful reaction, pyrrole and chloroform in the vapor phase at 500–550° gave 3-chloropyridine (33%) and a little 2-chloropyridine (2–5%).⁵³ No interconversion of the isomers occurred under these conditions, though pyrolytic rearrangement of *N*-alkylpyrrole to 3-substituted pyridines is considered to involve 2-alkylpyrroles as intermediates.⁵⁴ There is some independent evidence that dichlorocarbene is formed in the vapor phase decomposition of chloroform.⁵⁵

Under conditions more similar to those of the Reimer-Tiemann reaction 3-bromopyridine was obtained from pyrrole and bromoform.⁵⁶ Treatment of pyrrole with chloroform and aqueous alkali gave pyrrole-2-aldehyde⁵⁷; curiously, the formation of 3-chloropyridine under these conditions does not appear to have been reported, in spite of being frequently quoted. However, indole gave both indole-3-aldehyde and 3-chloroquinoline under these conditions⁵⁸ [Eq. (10)].



The Reimer-Tiemann reaction has also been used to formylate 2,5-dimethylpyrrole and its *N*-methyl derivative^{58a} and indoles having methyl, methoxyl, and phenyl substituents.⁵⁰ Significantly, 3-methylindole gave only 3-chloro-4-methylquinoline.⁵

⁵² E. R. Alexander, A. B. Herrick, and J. M. Roder, *J. Am. Chem. Soc.* **72**, 2760 (1950).

^{52a} Cf. W. G. Kofron, F. B. Kirby, and C. R. Hauser, *J. Org. Chem.* **28**, 873 (1963).

⁵³ H. L. Rice and T. E. Londergan, *J. Am. Chem. Soc.* **77**, 4678 (1955).

⁵⁴ A. Pictet, *Ber.* **38**, 1946 (1905); J. M. Patterson and P. Drenchko, *J. Org. Chem.* **27**, 1650 (1962).

⁵⁵ A. E. Shilov and R. D. Sabirova, *Dokl. Akad. Nauk SSSR* **114**, 1058 (1957); G. P. Semeluk and R. B. Bernstein, *J. Am. Chem. Soc.* **78**, 46 (1957).

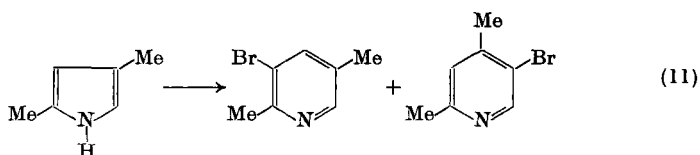
⁵⁶ G. L. Ciamician and P. Silber, *Ber.* **18**, 721 (1885).

⁵⁷ E. Bamberger and G. Djerdjian, *Ber.* **33**, 536 (1900).

⁵⁸ A. Ellinger, *Ber.* **39**, 2515 (1906).

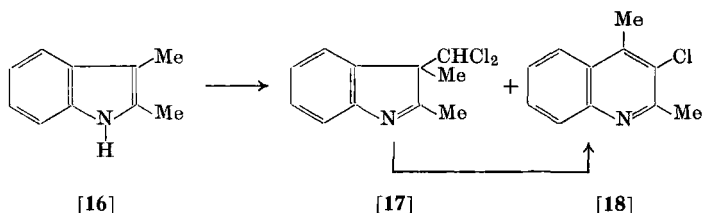
^{58a} O. Piloty, W. Krannich, and H. Will, *Ber.* **47**, 2531 (1914); E. Ghigi and A. Drusiani, *Atti Accad. Sci. Ist. Bologna, Classe Sci. Fis.* **11** [4], 14 (1956).

A variant of the Reimer-Tiemann reaction, using chloroform or bromoform with ethanolic sodium ethoxide, has been applied (mainly by Plancher and co-workers) to certain pyrroles and indoles with interesting results. Thus Bocchi⁵⁹ has shown that 2,5-dimethylpyrrole gave 3-halogeno-2,6-dimethylpyridine, and 2,4-dimethylpyrrole with bromoform gave two isomeric bromodimethylpyridines [Eq. (11)].



The latter reaction has been repeatedly misquoted (e.g. ref. 50) as involving 2,3-dimethylpyrrole, but the Reimer-Tiemann reaction of this pyrrole has not been investigated. In this case the methyl groups should activate the 2,3-bond sufficiently to make the 3-halogeno-2,4-dimethylpyridine the major—if not the sole—product.

Of particular interest in connection with the mechanism of these reactions was the isolation by Plancher and co-workers of dichloromethyl compounds in addition to the monochloro products of ring expansion; e.g., 2,3-dimethylindole (**16**) gave 3-dichloromethyl-2,3-dimethylindolenine (**17**) and 3-chloro-2,4-dimethylquinoline (**18**).⁶⁰

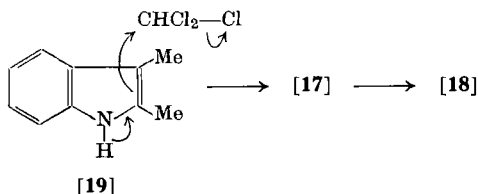


Furthermore they claimed that the dichloromethylindolenine **17** could be converted into the quinoline **18** by hot ethanolic sodium ethoxide. They also reported other similar cases of ring expansion of the dichloromethyl bases, with loss of hydrogen chloride, on further treatment with sodium ethoxide (cf. ref. 67). They considered that chloroform acted like a simple alkyl halide giving β -alkylation of the

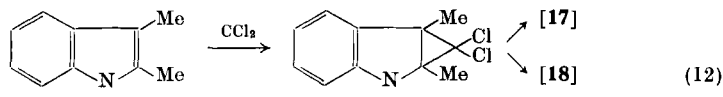
⁵⁹ O. Bocchi, *Gazz. Chim. Ital.* **30**, 89 (1900).

⁶⁰ G. Plancher and O. Carrasco, *Atti Accad. Naz. Lincei. Mem., Classe Sci. Fis., Mat. Nat., Sez. I* **13**, 575 (1904); **14**, 162 (1905).

indole nucleus (cf. **19**); assignment of the indolenine and pyrrolenine structures was based on this analogy, and it was assumed that these dichloro bases were intermediates in the ring expansion.



Interest in this reaction was revived when the relevance of a carbene mechanism was realized, particularly following the demonstration (cf. Section I, B) of a similar ring expansion of indene to 2-chloronaphthalene by dichlorocarbene *via* the cyclopropane adduct.^{12, 13} Indeed, at this time Nakazaki⁶¹ suggested that these reactions occurred by the addition of dichlorocarbene to the indolyl anion and subsequent rearrangement to the indolenine and, with loss of chloride ion, to the quinoline [Eq. (12)]. The preference of dichlorocarbene for



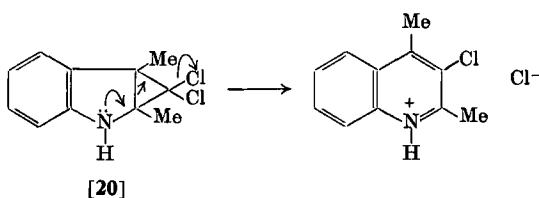
the double bond rather than the two nucleophilic centers of the ambident indolyl anion was not explained. In view of the known formation of dichlorocarbene under these Reimer-Tiemann conditions, and in the absence of good evidence for the indolenine structure and reasonable mechanistic justification for the indolenine-into-quinoline transformation, it was obviously tempting to consider that Plancher's indolenine (**17**) was in fact the dichlorocarbene adduct (**20**). Ring expansion then becomes entirely analogous to the conversion of indene into chloronaphthalene.^{50, 62, 63} However, two recent reinvestigations of the dimethylindole reaction by Robinson⁶² and Rees and Smithen⁶³ support Plancher's structural assignments for the reaction products, based on their chemical and spectral properties. This apparent

⁶¹ M. Nakazaki, *Nippon Kagaku Zasshi* **76**, 1169 (1955).

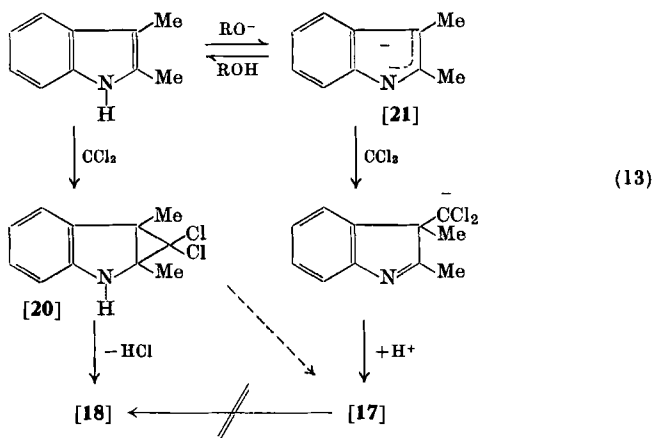
⁶² B. Robinson, *Tetrahedron Letters* **4**, 139 (1962).

⁶³ C. W. Rees and C. E. Smithen, *Chem. Ind. (London)* 1022 (1962); *J. Chem. Soc.* 928, 938 (1964). C. E. Smithen, Ph.D. Thesis, London, 1963.

anomaly has been resolved by the demonstration that, contrary to Plancher and Carrasco's findings,⁶⁰ the dichloromethylindolenine (**17**) is *not* converted into the quinoline (**18**) under the reaction conditions, nor under more vigorous basic conditions, nor by boiling with silver nitrate in methyl cyanide, which would be more likely to effect this transformation.⁶³ Thus the indolenine need be considered no longer as an intermediate in the reaction. Several sources of dichlorocarbene have been used in this reaction and all give both products, though in

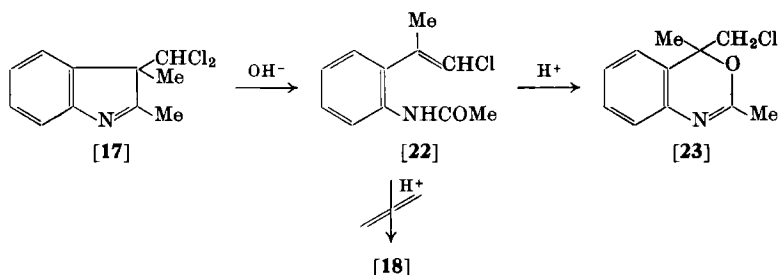


varying proportions; in particular, formation of the indolenine (**17**) at the expense of the quinoline (**18**) is favored the more strongly basic the conditions. The yield of both products was decreased ten-fold in the presence of cyclohexene. Dibromocarbene, generated in various ways, including boiling sodium tribromoacetate in 1,2-dimethoxyethane, gave very similar results, while difluorocarbene, from ethyl chlorodifluoroacetate and potassium *t*-butoxide, gave only 3-difluoromethyl-2,3-dimethylindolenine, the structure of which was confirmed by its N.M.R. spectrum.⁶³ The simplest mechanism consistent with these, and other, data is considered to be that summarized by Eq. (13).^{62, 63} The



chloroquinoline (**18**) arises only from addition of dichlorocarbene to the neutral dimethylindole molecule followed by ring expansion of the adduct (**20**), which has not been isolated. The dichloromethylindolenine (**17**) is formed by electrophilic attack of the carbene at the 3-position of the ambident indolyl anion (**21**). Formation of the indolenine by an alternative mode of rearrangement of the adduct (**20**) probably makes only a minor contribution, at most.

Under the conditions of the attempted conversion of the indolenine **17** into the quinoline **18** most of the indolenine was recovered, but there was also formed a small amount of a hydrolysis product, *o*-acetamido- β -chloro- α -methylstyrene (**22**), obtainable in good yield with aqueous ethanolic potassium hydroxide.⁶³ By analogy with a similar sequence of reactions in the carbocyclic series⁶⁴ the hydrolysis product **22** might possibly undergo acid-catalyzed cyclodehydration to the quinoline



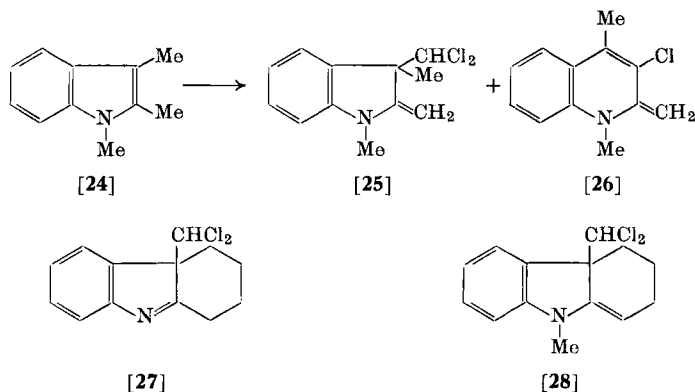
(**18**), and such a route for the conversion of the indolenine into the quinoline was proposed by Wynberg⁵⁰; however, Rees and Smithen⁶³ find that the amide (**22**) is isomerized by acid to 4-chloromethyl-2,4-dimethyl-3,1-benzoxazine (**23**).

The structure of the product⁶⁵ of the Reimer-Tiemann reaction of 1,2,3-trimethylindole (**24**) has been confirmed as 3-dichloromethyl-1,3-dimethyl-2-methyleneindoline (**25**) by spectroscopy and oxidation to the *N*-methyloxindole; when the dichlorocarbene was generated under neutral conditions a ring-expanded product, 3-chloro-1,4-dimethyl-2-methylene-1,2-dihydroquinoline (**26**) could be isolated and oxidized to the corresponding α -quinolone.⁶³ These reactions presumably proceed by mechanisms similar to those discussed for 2,3-di-

⁶⁴ R. M. Dodson, J. R. Lewis, W. P. Webb, E. Wenkert, and R. D. Youssefyeh, *J. Am. Chem. Soc.* **83**, 938 (1961).

⁶⁵ G. Plancher and O. Carrasco, *Atti Accad. Naz. Lincei, Mem., Classe Sci. Fis., Mat. Nat., Sez. I* **14**, 705 (1905).

methylindole, a (allylic) proton of the 2-methyl group being lost in the absence of a proton on the hetero atom. In the reaction of tetrahydrocarbazole^{62, 66} and *N*-methyltetrahydrocarbazole⁶³ with dichlorocarbene only the dichloromethyl bases **27** and **28**, respectively, were



isolated, ring expansion being prohibited by the steric constraint of the cyclohexane ring. The general mechanistic considerations applied to the above indoles presumably apply equally to the pyrrole-into-pyridine transformations since, again, the reported⁶⁷ conversion of the pyrrolenine obtained from 2,5-dimethylpyrrole into the corresponding pyridine could not be repeated.⁶³ The β -pyrrolenine structures favored by Plancher for the Reimer-Tiemann products from alkyl pyrroles, by analogy with the supposed β -alkylation of pyrroles, should presumably be revised to the α -pyrrolenine structures; in a recent reinvestigation of the alkylation of pyrrole and its methyl homologues the pentamethyl base was shown to be the 2,2,3,4,5-isomer.⁶⁸

With monochlorocarbene, pyrrole and indole underwent ring expansion to pyridine and quinoline, respectively,^{68a} and 2,3-dimethylindole similarly gave 2,4-dimethylquinoline.⁶³

⁶⁶ M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.* **80**, 126 (1958).

⁶⁷ G. Plancher and U. Ponti, *Atti Accad. Naz. Lincei, Mem., Classe Sci. Fis., Mat. Nat., Sez. II* **18**, 469 (1909); G. Plancher and T. Zambonini, *ibid.* **II**, **22**, 712 (1913).

⁶⁸ H. Booth, A. W. Johnson, E. Markham, and R. Price, *J. Chem. Soc.* 1587 (1959); H. Booth, A. W. Johnson, F. Johnson, and R. A. Langdale-Smith, *ibid.* 650 (1963).

^{68a} G. L. Closs and G. M. Schwartz, *J. Org. Chem.* **26**, 2609 (1961).

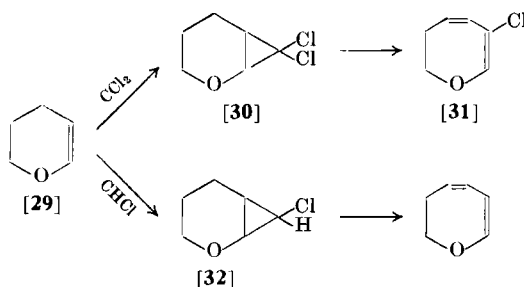
C. OTHER FIVE-MEMBERED SYSTEMS

Very few reactions of carbenes with heterocyclic systems containing more than one hetero atom have been studied. They are confined to variants of the Reimer-Tiemann formylation of thiazoles,⁶⁹ pyrazoles,⁷⁰ iminazoles,⁷¹ and indolizines,⁷² and ring expansion does not appear to have been observed.

III. Reactions with Six-Membered Heterocyclic Rings

A. OXYGEN AND SULFUR SYSTEMS

The reactions of halocarbenes with several six-membered oxygen and sulfur heterocyclics have been investigated by Parham and co-workers as a new synthetic route to the related seven-membered rings, following the successful formation of some dihydrooxepins from the dihydropyran **29**.⁷³ The adduct **30** gave 6-chloro-2,3-dihydrooxepine (**31**) in good yield on pyrolysis in quinoline. The monochloro-carbene adduct (**32**) was separated into *endo*- and *exo*-isomers, only one of which underwent ring expansion upon heating in quinoline.



This is consistent with neighboring group participation by the oxygen atom in the separation of the chloride ion.⁷³

However, the presence of a fused benzene ring was found to limit the scope of this type of ring expansion severely. Thus the dichloro-carbene adducts of both *2H*- (**33**) and *4H*-chromen (**34**) failed to rearrange to 2,3-benzoxepines (**35**) on heating.⁷⁴ Although some

⁶⁹ E. Ochiai and F. Nagasaka, *Ber.* **72**, 1470 (1939).

⁷⁰ G. Losco, *Gazz. Chim. Ital.* **70**, 284 (1940).

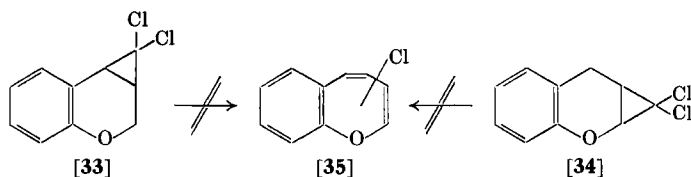
⁷¹ H. Heath, A. Lawson, and C. Rimington, *J. Chem. Soc.* 2223 (1951).

⁷² E. D. Rossiter and J. E. Saxton, *J. Chem. Soc.* 3654 (1953).

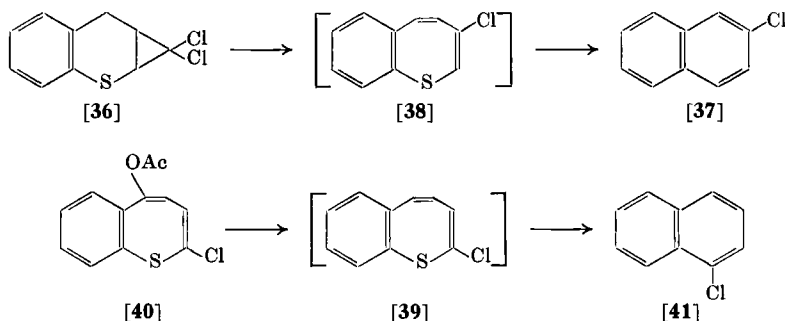
⁷³ E. F. Schweizer and W. E. Parham, *J. Am. Chem. Soc.* **82**, 4085 (1960).

⁷⁴ W. E. Parham and L. D. Huestis, *J. Am. Chem. Soc.* **84**, 813 (1962).

chloride ions were liberated under vigorous conditions, the nature of the other products is unknown. 4*H*-Thiachromen gave the normal adduct (**36**) with dichlorocarbene but this unexpectedly gave 2-chloronaphthalene (**37**) in boiling quinoline.⁷⁵ The fate of the sulfur was not determined, although some hydrogen sulfide was detected. The



formation of 6-chloro-2,3-benzothiepine (**38**) as an intermediate cannot be excluded since it is probable that this would undergo sulfur extrusion under the vigorous reaction conditions. This is supported by the recent report that on attempted synthesis of 7-chloro-2,3-benzothiepine (**39**) by pyrolysis of the acetate (**40**) the products obtained were 1-chloronaphthalene (**41**) and di-(1-naphthyl) disulfide.⁷⁶

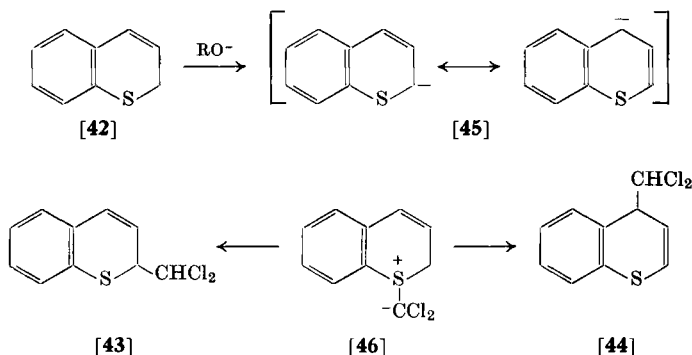


The reaction of dichlorocarbene with 2*H*-thiachromen (**42**) was exceptional since it gave none of the expected adduct but rather the products of substitution at the 2- (**43**) and 4-position (**44**) together with a "bis-adduct" of unknown structure.⁷⁵ The substitution products could arise by reaction of the ambident anion **45** with dichlorocarbene, but the absence of these products in the same reaction of 4*H*-thiachromen argues against this mechanism. The

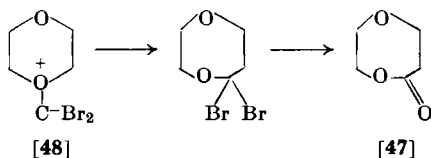
⁷⁵ W. E. Parham and R. Koncos, *J. Am. Chem. Soc.* **83**, 4034 (1961).

⁷⁶ V. J. Traynelis and J. R. Livingston, Abstr. of Papers, 142nd Meeting, Am. Chem. Soc., Atlantic City, N.J., Sept. 1962, p. 34-Q.

initial formation of the sulfur ylide (**46**) with subsequent rearrangement to **43** and **44** was tentatively proposed to explain this anomalous reaction.⁷⁵ The reaction of silver nitrate with bromoform in



aqueous dioxane gave the lactone **47** in 35% yield, the formation of which may be rationalized as attack by dibromocarbene or the dibromomethyl carbonium ion at the ethereal oxygen, followed by rearrangement of the ylide **48** and hydrolysis.⁷⁷ The related ylide



mechanism for the reaction of diazomethane with tetrahydrofuran to give 2-methyl- and 3-methyl-tetrahydrofuran has now been discounted, however, since no tetrahydropyran could be detected.⁷⁸

B. NITROGEN SYSTEMS

The Reimer-Tiemann formylation of several phenols in the quinoline and pyrimidine series is known, but the reaction is unsuccessful with hydroxypyridines; 3-hydroxypyridine gave a polymer.⁷⁹ No 2-hydroxyquinoline appears to have been studied; the 4-hydroxy

⁷⁷ F. Badea and C. D. Nenitzescu, *Angew. Chem.* **72**, 415 (1960).

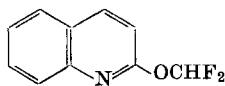
⁷⁸ W. von E. Doering, L. H. Knox, and M. Jones, *J. Org. Chem.* **24**, 136 (1959).

⁷⁹ D. Westmark, quoted by H. Wynberg, ref. 50.

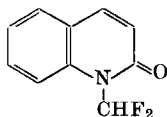
isomer gave the 3-aldehyde⁸⁰ and 4-hydroxy-2-methylquinoline gave the 3-aldehyde plus an alkali-insoluble compound, $C_{31}H_{25}N_3O_3$, m.p. 192° , which reverted to starting material on long boiling in water.⁸¹ This product is probably the ortho-ester $(RO)_3CH$, where $R = 2$ -methyl-4-quinolinyl. 2,4-Dihydroxyquinoline gave the 3-aldehyde,⁸² and 6- and 7-hydroxyquinoline gave only the 5-⁸³ and 8-aldehydes,⁸⁴ respectively. 8-Hydroxyquinoline gave both the 5- and 7-aldehydes,⁸⁵ unlike 1-naphthol which has not been successfully formylated,⁵⁰ and 8-hydroxy-7-methylquinoline gave the 5-aldehyde.⁸⁶

2-Substituted-4-hydroxy-6-methylpyrimidines are formylated in the 5-position when the 2-substituent (e.g. NH_2 , OH) is sufficiently electron releasing.^{87, 88} The related 4-mercapto compounds gave only the ortho-thio-esters.⁸⁷

Treatment of the sodium salt of carbostyryl with chlorodifluoromethane and sodium *t*-butoxide in 1,2-dimethoxyethane gave the products of *O*- (49) and *N*-alkylation (50).⁸⁹



[49]



[50]

There are a few scattered references to the reaction of nonphenolic six-membered heterocyclics with dichlorocarbene under Reimer-Tiemann conditions. Thus a mixture of 2-methylpyridine, chloroform, and sodium hydroxide is reported to contain sorbic acid and cyanide ions after standing for several months.⁹⁰ Another similar reaction of

⁸⁰ B. Bobranski, *Ber.* **68**, 1113 (1936); L. R. Morgan, R. J. Schunior, and J. H. Boyer, *J. Org. Chem.* **28**, 260 (1963).

⁸¹ M. Conrad and L. Limpach, *Ber.* **21**, 1972 (1888).

⁸² Y. Asahina and M. Inubuse, *Ber.* **65**, 61 (1932).

⁸³ B. Bobranski, *J. Prakt. Chem.* **134**, 141 (1932).

⁸⁴ L. Kochanska and B. Bobranski, *Ber.* **69**, 1807 (1936).

⁸⁵ R. N. Sen and S. K. Ray, *J. Indian Chem. Soc.* **9**, 173 (1932).

⁸⁶ C. Hamada, K. Isogai, and Y. Nakajima, *Nippon Kagaku Zasshi* **82**, 1284 (1961).

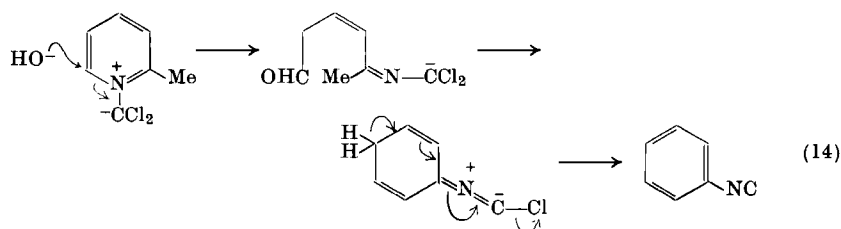
⁸⁷ R. Hull, *J. Chem. Soc.* 4845 (1957).

⁸⁸ R. H. Wiley and Y. Yamamoto, *J. Org. Chem.* **25**, 1906 (1960).

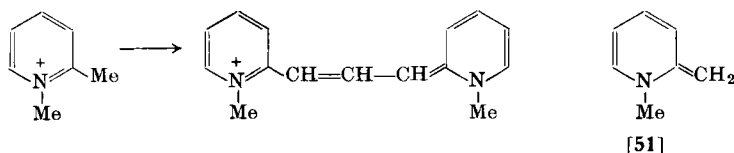
⁸⁹ T. Y. Shen, S. Lucas, and L. H. Sarett, *Tetrahedron Letters* **2**, 43 (1961).

⁹⁰ W. König, *J. Prakt. Chem.* **83**, 406 (1911), reported by H. S. Mosher, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. I, p. 433. Wiley, New York, 1950.

considerable interest has been described by Ploquin⁹¹: pyridines having a methyl group in the 2- or 4-position give phenylisocyanides when treated with chloroform and concentrated alkali. Thus 2-methylpyridine is converted into phenylisocyanide; this reaction may proceed by base-catalyzed ring opening of the ylide formed by attack of dichlorocarbene on the nitrogen atom, followed by recycelization onto the active methyl group [Eq. (14)]. The mechanisms for the alleged transformations⁹¹ of 4-methylpyridine into phenylisocyanide and of 2-methylquinoline into 2-naphthylisocyanide are more obscure and worthy of investigation.



2-Methyl- and 4-methyl-pyridinium methiodides yield cyanine-type dyes with chloroform and alcoholic potassium hydroxide,⁹² e.g. *via* the methylene dihydropyridine (**51**) with attack by dichlorocarbene at the active methylene group (cf. ref. 92a).



Dichlorocarbene, generated in a variety of ways, was shown to deoxygenate pyridine *N*-oxide, being itself oxidized to phosgene.^{92b}

Most reactions of diazomethane with these heterocyclic systems involve attack at other functional groups (for a review see ref. 1), such as in the *O*- and *N*-methylation of the hydroxy-pyridines and -quino-

⁹¹ J. Ploquin, *Bull. Soc. Chim. France* 901 (1947).

⁹² E. Rosenhauer and F. Barlet, *Ber.* **62**, 2724 (1929).

^{92a} A. P. Krapcho, P. S. Huyffer, and I. Starer, *J. Org. Chem.* **27**, 3096 (1962);

A. P. Krapcho and P. S. Huyffer, *ibid.* **28**, 2461 (1963).

^{92b} E. E. Schweizer and G. J. O'Neil, *J. Org. Chem.* **28**, 2460 (1963).

lines.⁹³ An exception is the photolysis of diazomethane in pyridine to give 2-methylpyridine as the only product. This is not consistent with direct electrophilic substitution but may involve attack by methylene at the nitrogen atom followed by intramolecular rearrangement of the ylide.⁹⁴ Pyridine, quinoline, and isoquinoline are converted into their *N*-methyl quaternary salts by a fluoroboric acid catalyzed reaction with diazomethane, the fluoroborate anions being very weakly nucleophilic.⁹⁵ The authors suggest a similar mechanism for the formation of *N*-phenacyl quaternary salts from pyridinium and isoquinolinium salts and diazoacetophenone.⁹⁶ Ethyl diazoacetate reacts with 2-pyridones on pyrolysis to give mixtures of *O*- and *N*-alkylated products.⁹⁷

⁹³ H. Meyer, *Monatsh. Chem.* **26**, 1311 (1905); J. P. Phillips and R. W. Keown, *J. Am. Chem. Soc.* **73**, 5483 (1951).

⁹⁴ R. Daniels and O. L. Saterni, *Proc. Chem. Soc.* 286 (1960).

⁹⁵ R. Daniels and C. G. Kormendy, *J. Org. Chem.* **27**, 1860 (1962).

⁹⁶ L. C. King and F. M. Miller, *J. Am. Chem. Soc.* **70**, 4154 (1948).

⁹⁷ J. Maas, G. B. R. de Graaff, and H. J. den Hertog, *Rec. Trav. Chim.* **74**, 175 (1955); M. P. Cava and N. K. Bhattacharyya, *J. Org. Chem.* **23**, 1614 (1958).

The Carbolines

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I. Introduction

This review is an attempt to collect under one heading and to present in a systematic manner the large body of work which deals with the chemistry of the carboline ring systems. Some three hundred papers in this field have been published during the last decade, more than twice as many as appeared during the preceding fifty years. The renewed interest in the chemistry of the carbolines is due in no small measure to the discovery of serotonin and to the recent developments in the chemistry and pharmacology of the Rauwolfia and related alkaloids.

It is not proposed to discuss these topics, which have been adequately reviewed elsewhere, but to focus attention on general aspects of carboline chemistry, including relevant findings which emerged incidentally in the course of degradative and synthetic work in the field of indole alkaloid chemistry. The only published review on the carbolines¹ emphasizes aspects of the work carried out prior to 1950.

In the present review the literature to the end of 1962 has been covered. Synthetic methods leading to the different oxidation states of the carboline ring systems, as well as methods for the interconversion of these different oxidation states, are summarized. The reactions at carbon and at nitrogen of fully aromatic carbolines and their reduced and oxidized derivatives are reviewed. Nuclear rearrangements and methods for extending the tricyclic system to four and five rings are surveyed, and a discussion of the structure and chemistry of pseudo- and anhydro-bases derived from carbolines is presented. A review of the biogenesis and biosynthesis of naturally occurring simple carbolines and a résumé of spectral data conclude this report.

II. Nomenclature

The nomenclature used to describe the fused benzene-pyrrole-pyridine system of the compounds under discussion has been repeatedly modified, and the compounds have been numbered in an astonishing variety of ways since Perkin and Robinson² introduced the name carboline for the ring system, which was encountered for the first time in the harmala alkaloids. In the earliest version of carboline nomenclature, the parent compound of the series, whose trivial name was norharman, was referred to as 4-carboline and numbered as in **1**. Harmine (**2**) then became 11-methoxy-3-methyl-4-carboline.

The anhydro-bases (**3**) derived from quaternary salts of 4-carboline by treatment with alkali were designated as isocarbolines² or ψ -carbolines.³

The numbering of the carboline system was later modified⁴ to that shown in **4**, and the position of the basic nitrogen in the pyridine ring was designated by a Greek letter. Harmine thus became 8-methoxy-2-

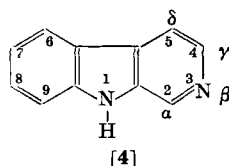
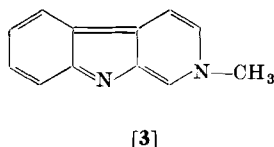
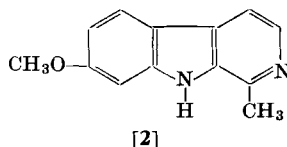
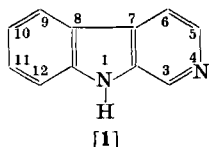
¹ W. O. Kermack and J. E. McKail, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, p. 237. Wiley, New York, 1961.

² W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **115**, 967 (1919).

³ W. O. Kermack and R. H. Slater, *J. Chem. Soc.* 789 (1928).

⁴ J. M. Gulland, R. Robinson, J. Scott, and S. Thornley, *J. Chem. Soc.* 2924 (1929).

methyl- β -carboline. The same system of numbering has been used without Greek letters (harminine = 8-methoxy-2-methyl-3-carboline).^{5, 6} The Greek letters have also been used in conjunction with the original system of numbering (harminine = 11-methoxy-3-methyl- β -carboline).⁷



According to the "Ring Index,"⁸ the system is classified as pyridoindole and numbered as in **6** (harminine = 7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole). This is the nomenclature adopted by *Chemical Abstracts*, according to which α -carboline (**5**) is 9*H*-pyrido[2,3-*b*]indole, β -carboline (**6**) is 9*H*-pyrido[3,4-*b*]indole, γ -carboline (**7**) is 5*H*-pyrido[4,3-*b*]indole, and δ -carboline (**8**) is 5*H*-pyrido[3,2-*b*]indole.

The numbering used in **6** was introduced also in conjunction with the carboline nomenclature⁹ (harminine = 7-methoxy-1-methyl- β -carboline). This is the system which, at the present time, appears to be most widely adopted.¹⁰ The same numbering has been used without the Greek letter convention¹¹ (harminine = 7-methoxy-1-methyl-2-carboline).

Further variants are to be found in the literature. β -Carboline has been referred to as 2,9-diazafluorene (entry in the Subject Index of

⁵ K. Eiter and A. Nezval, *Monatsh. Chem.* **81**, 404 (1950).

⁶ B. Witkop, *J. Am. Chem. Soc.* **75**, 3361 (1953).

⁷ A. D. Mitchell, "British Chemical Nomenclature," p. 120. Arnold and Co., London, 1948.

⁸ A. M. Patterson and L. T. Capell, "The Ring Index," 2nd Edn. American Chemical Society, 1960.

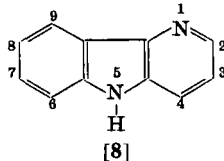
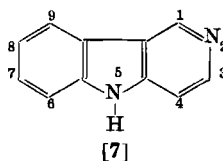
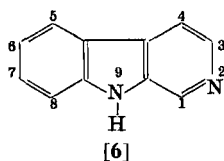
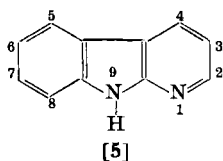
⁹ A. A. Morton, "The Chemistry of Heterocyclic Compounds." McGraw-Hill, New York, 1946.

¹⁰ R. S. Cahn, *J. Chem. Soc.* 5061 (1952).

¹¹ W. M. Whaley and T. R. Govindachari, *Org. Reactions* **6**, 74 (1951).

Chemical Abstracts), and α -carboline is sold commercially under the name 1-azacarbazole. The trivial norharman nomenclature, in conjunction with numbering as in **1**¹² or as in **6**,¹³ is still to be found in recent papers. Other systems of numbering,¹⁴ as well as some incorrect systems of nomenclature,¹⁵ are to be found and add to the confusion.

In the present review the carboline, rather than the pyridoindole, nomenclature is adopted with the numbering for α -, β -, γ -, and δ -carbolines shown in structures **5**–**8**, respectively, as recommended by the Editor of the *Journal of the Chemical Society* in his Report on Nomenclature, 1952,¹⁰ and by the Definitive I.U.P.A.C., 1957, rules of organic nomenclature (Rule B—2.11).^{15a} In the interest of clarity,



the indole nitrogen atom (9 in α - and β -, 5 in γ - and δ -carbolines) and the pyridine nitrogen atom (1 in α - and δ -, 2 in β - and γ -carbolines) will be referred to as *ind-N* and *pyr-N*, respectively, when discussion is focused on the nitrogen atoms of the carboline system. Anhydrobases derived from quaternary carbolinium salts will be referred to as such, and not as *iso*- or *ψ* -carbolines.

¹² J. Le Men and C. Fan, *Bull. Soc. Chim. France* 1866 (1959).

¹³ M. Protiva, J. O. Jílek, E. Hachová, L. Novák, Z. J. Vejdělek, and E. Adlerová, *Collection Czech. Chem. Commun.* **24**, 74 (1959).

¹⁴ V. Boekelheide and C. Ainsworth, *J. Am. Chem. Soc.* **72**, 2132 (1950).

¹⁵ Z. Pelchowicz and E. D. Bergmann, *J. Chem. Soc.* 4699 (1960).

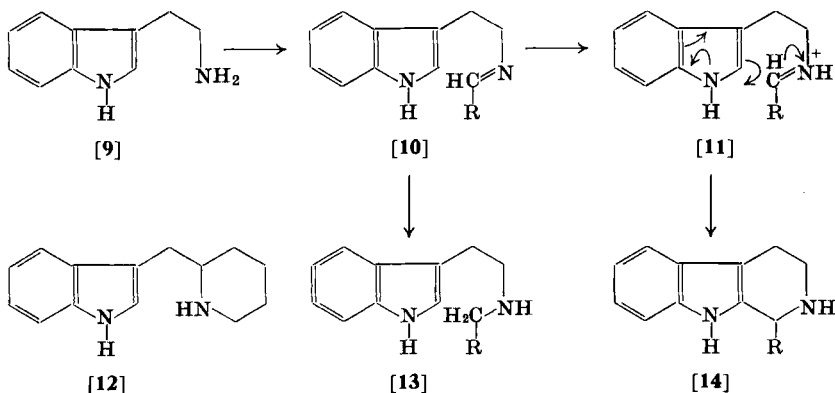
^{15a} Using this system of nomenclature the compounds which are most commonly encountered in the older literature and are there designated by trivial names are described as follows: harmine = 7-methoxy-1-methyl- β -carboline, harmol = 7-hydroxy-1-methyl- β -carboline, harman = 1-methyl- β -carboline, norharmine = 7-methoxy- β -carboline, norharman = β -carboline, harmaline = 7-methoxy-1-methyl-3,4-dihydro- β -carboline, harmalol = 7-hydroxy-1-methyl-3,4-dihydro- β -carboline, and harmalan = 1-methyl-3,4-dihydro- β -carboline.

III. Synthesis

A. TETRAHYDROCARBOLINES

1. From Non-Carboline Precursors

a. *Mannich Reactions.* The earliest general route to the 1,2,3,4-tetrahydro- β -carboline system, first described by Tatsui^{16, 17} and by Akabori and Saito,¹⁸ was modelled on the Pictet-Spengler tetrahydroisoquinoline synthesis.¹⁹ In its simplest form the synthesis consists of the acid-catalyzed Mannich reaction of acetaldehyde with tryptamine (9) in which the latter supplies the nucleophilic as well as the basic center, yielding 1-methyl-1,2,3,4-tetrahydro- β -carboline (14; R = CH₃). This reaction takes place most readily in the presence of dilute mineral acid, at pH 1, but condensation occurs even under "pseudo-physiological" conditions, i.e., at room temperature at a pH range near neutrality.²⁰ Substituted tryptamines (*ind-N*-alkyl,²¹ *N* β -methyl,^{22, 23} 5-methoxy,²⁴ 6-methoxy,¹⁸ 5-fluoro,¹⁵ and the side-chain-substituted derivative 12²⁵) also yield the expected products with acetaldehyde.



¹⁶ G. Tatsui, *J. Pharm. Soc. Japan* **48**, 453 (1928); *Chem. Abstr.* **22**, 3415 (1928).

¹⁷ G. Tatsui, *J. Pharm. Soc. Japan* **49**, 749 (1929); *Chem. Abstr.* **24**, 125 (1930).

¹⁸ S. Akabori and K. Saito, *Ber.* **63**, 2245 (1930).

¹⁹ W. M. Whaley and T. R. Govindachari, *Org. Reactions* **6**, 151 (1951).

²⁰ G. Hahn and H. Ludewig, *Ber.* **67**, 2031 (1934).

²¹ U. Hörlein, *Chem. Ber.* **87**, 463 (1954).

²² G. Barger, A. Jacob, and J. Madinaveitia, *Rec. Trav. Chim.* **57**, 548 (1938).

²³ N. K. Yurashevski, *Zh. Obshch. Khim.* **11**, 157 (1941).

²⁴ W. M. McIsaac, *Biochim. Biophys. Acta* **52**, 607 (1961).

²⁵ V. Boekelheide and Chu-Tsin Liu, *J. Am. Chem. Soc.* **74**, 4920 (1952).

A few other aldehydes have been used in the reaction, either under normal or "pseudo-physiological" conditions. Of these, glycolaldehyde,²⁶ 5-hydroxypentanal,²⁷ phenylacetaldehyde,²⁰ and benzaldehyde²⁸ condense readily, but hydroxy and methoxy derivatives of these aromatic aldehydes give the product in poor yield,^{28, 29} presumably due to their instability, as evidenced by their tendency to undergo self-condensation in acid solution.^{29, 30} Reaction with phthaldehydic acids, such as opianic acid, proceeded readily,³¹ whereas reaction with chloral did not occur.¹⁷

One instance of an intramolecular Mannich reaction of an *N*_β-acyl-tryptamine has been reported.³²

A protonated Schiff's base (**11**) is the presumed intermediate in the Mannich reaction. From the condensation of tryptamine with benzaldehyde a Schiff's base (**10**; R = C₆H₅) has indeed been isolated,³³ which on treatment with acid cyclizes to 1-phenyl-1,2,3,4-tetrahydro-β-carboline (**14**; R = C₆H₅).¹³ Condensation of a tryptamine derivative with an aldehyde in the absence of acid leads to the corresponding Schiff's base (**10**),³⁴ the structure of which has been proved by reduction to an *N*_β-alkyltryptamine derivative (**13**) with sodium borohydride.^{34, 35} Reconversion of a 1,2,3,4-tetrahydro-β-carboline (**14**; R = CH₂C₆H₃-3,4-(OH)₂) into the corresponding protonated Schiff's base of tryptamine (**11**) has been postulated as a step in the rearrangement in strong acid of this 1,2,3,4-tetrahydro-β-carboline derivative into an indolenine³⁶ (see Section IV, B, 3). One instance of a Mannich-type condensation of an aldehyde with a modified tryptamine derivative into the β-position, rather than into the α-position, of the indole

²⁶ I. D. Spenser, *Can. J. Chem.* **37**, 1851 (1959).

²⁷ L. H. Groves and G. A. Swan, *J. Chem. Soc.* 650 (1952).

²⁸ G. Hahn, L. Bärwald, O. Schales, and H. Werner, *Ann. Chem.* **520**, 107 (1935).

²⁹ H. Plieninger and B. Kiefer, *Chem. Ber.* **90**, 617 (1957).

³⁰ E. Späth, F. Kuffner, and F. Keszler, *Ber.* **69**, 378 (1936).

³¹ S. Wawzonek, and G. E. Nelson, *J. Org. Chem.* **27**, 1377 (1962).

³² E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Am. Chem. Soc.* **80**, 5006 (1958).

³³ T. Hoshino and Y. Kotake, *Ann. Chem.* **516**, 76 (1935).

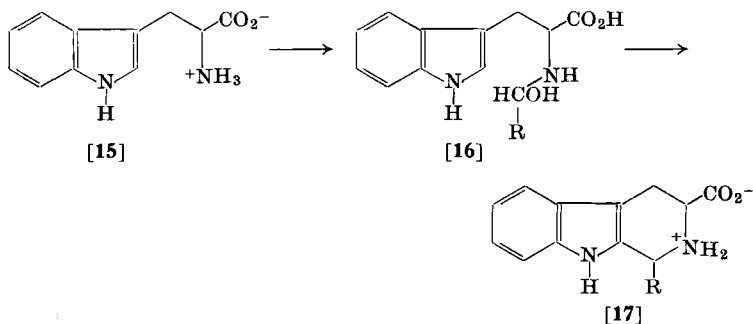
³⁴ R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *J. Am. Chem. Soc.* **78**, 2023 (1956); *Tetrahedron* **2**, 1 (1958).

³⁵ J. Weichet, K. Pelz, and L. Bláha, *Collection Czech. Chem. Commun.* **26**, 1529 (1961).

³⁶ J. Harley-Mason and W. R. Waterfield, *Chem. Ind. (London)* 1477 (1960); *Tetrahedron* **19**, 65 (1963).

nucleus has been reported, and a carbinolamine intermediate was isolated.³⁷

Tryptophan (15) and its substituted derivatives also react with aldehydes to give 1,2,3,4-tetrahydro- β -carboline-3-carboxylic acids (17). Acetaldehyde and benzaldehyde yield the expected products with the amino acid^{38, 39} and its N_{β} -methyl derivative (abrine).^{38, 40}



Other aldehydes which have been used in the reaction are propanal,^{41, 42} butanal,⁴³ glycolaldehyde,⁴⁰ 3-hydroxybutanal,³⁸ and a number of phenylacetaldehyde³⁹ and benzaldehyde^{31, 39} derivatives. Whereas condensation of tryptophan with acetaldehyde takes place even at room temperature and pH 6.7,⁴⁴ the reactions with chloral, chloroacetaldehyde,³⁹ and crotonaldehyde³⁸ fail entirely.

Acetaldehyde has been used in the condensation with a large number of substituted tryptophans, including the 4-⁴⁵ 5-^{46, 47} 6-⁴⁴ and 7-methoxy^{45, 47}; 4-methoxy-1-methyl⁴⁸ and 5-methoxy-1-methyl⁴⁶;

³⁷ E. E. van Tamelen, L. J. Dolley, and R. G. Lawton, *Tetrahedron Letters* No. 19, 30 (1960).

³⁸ W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **113**, 759 (1936).

³⁹ H. R. Snyder, C. H. Hansch, L. Katz, S. M. Parmenter, and E. C. Spaeth, *J. Am. Chem. Soc.* **70**, 219 (1948).

⁴⁰ D. G. Harvey, E. J. Miller, and W. Robson, *J. Chem. Soc.* 153 (1941).

⁴¹ N. J. Leonard and R. C. Elderfield, *J. Org. Chem.* **7**, 556 (1942).

⁴² R. Tschesche and H. Jenssen, *Chem. Ber.* **93**, 271 (1960).

⁴³ A. P. Gray, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.* **76**, 2792 (1954).

⁴⁴ D. G. Harvey and W. Robson, *J. Chem. Soc.* 97 (1938).

⁴⁵ G. G. Doig, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.* 3912 (1952).

⁴⁶ J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.* 1203 (1951).

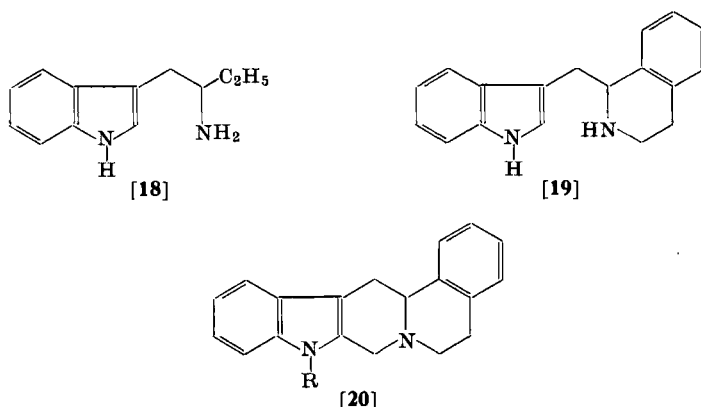
⁴⁷ R. H. Marchant and D. G. Harvey, *J. Chem. Soc.* 1808 (1951).

⁴⁸ J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.* 3904 (1952).

7-methyl and 1,7-dimethyl⁴⁹; and 5-bromo^{50, 51} and 5-iodo⁵² derivatives.

The ethyl ester of the tetrahydrocarbolinecarboxylic acid derived from *dl*-tryptophan and acetaldehyde has been resolved into its four stereoisomers.¹²

The reactions of tryptophan and of tryptamine derivatives with formaldehyde require special comment. Whereas tryptamine and its 5- and 7-methoxy and *ind-N*-methyl⁵³ and -ethyl derivatives⁴¹ react



normally with formaldehyde, the side-chain substituted tryptamine **18** did not react,¹⁴ and the derivative **19** yielded the *ind-N*-hydroxymethylcarboline (**20**; R = CH₂OH) in addition to the normal product (**20**; R = H).²⁵ An analogous *ind-N*-hydroxymethylcarboline derivative was also obtained on treatment of the tryptamine derivative **21** with formaldehyde.⁵⁴

ind-N-Formylation has also been reported⁵⁵ to take place in the case of *N*_β-methyltryptamine, which on treatment with formaldehyde in acid solution yields 2-methyl- and 9-hydroxymethyl-2-methyl-1,2,3,4-tetrahydro-β-carboline plus a third product, to which the sterically unlikely structure **22** was assigned. Inspection of a molecular

⁴⁹ J. W. Cook, R. M. Gailey, and J. D. Loudon, *J. Chem. Soc.* 568 (1954).

⁵⁰ H. R. Snyder, S. M. Parmerter, and L. Katz, *J. Am. Chem. Soc.* **70**, 222 (1948).

⁵¹ D. G. Harvey, *J. Chem. Soc.* 473 (1959).

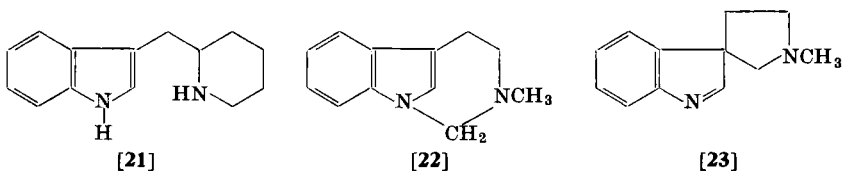
⁵² D. G. Harvey, *J. Chem. Soc.* 3760 (1958).

⁵³ E. Späth and E. Lederer, *Ber.* **63**, 2102 (1930).

⁵⁴ H. Bader and W. Oroshnik, *J. Am. Chem. Soc.* **79**, 5686 (1957).

⁵⁵ N. K. Yurashevski, *J. Gen. Chem. USSR (Eng. Transl.)* **24**, 737 (1954).

model shows that ring closure to **22** would impose very large strain on the planar indole system. It seems far more likely that, if ring closure has indeed taken place in the formation of this product, a β -cyclized compound (**23**) is formed. This interesting possibility requires re-investigation.



In the competition between Pictet-Spengler ring closure and Escheiwer methylation of tryptamine derivatives on treatment with formaldehyde in formic acid, ring closure appears to be favored at pH < 7, but pH cannot be the only controlling factor.⁵⁴ An instance of ring closure, followed by formylation at the *pyr-N* of the resulting tetrahydro- β -carboline, has also been reported under Escheiwer conditions.⁵⁶ Related to this is the finding that in a reaction mixture containing tryptamine, formaldehyde, and a β -keto ester, 1,2,3,4-tetrahydro- β -carboline is formed in the presence of acid, but in the absence of acid an intermolecular Mannich reaction, yielding a tryptamine derivative, takes place preferentially.⁵⁷

Depending on conditions, formaldehyde and tryptophan yield either 1,2,3,4-tetrahydro- β -carboline-3-carboxylic acid (**17**; R = H),^{38, 40, 58} or the intermediate carbinolamine (**16**, R = H), which is readily converted into the cyclized product.^{40, 58, 59} This compound reacts further with formaldehyde, presumably to yield the *ind-N*-hydroxymethyl derivative.⁶⁰ Similarly two products were obtained on treatment of *N* β -methyltryptophan with formaldehyde,⁴⁰ but only the expected tetrahydrocarboline derivative was obtained from *N* β -methyltryptophan-4-carboxylic acid.⁶¹ It is noteworthy that the

⁵⁶ A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph, *J. Chem. Soc.* 3388 (1959).

⁵⁷ E. E. van Tamelen and C. Placeway, *J. Am. Chem. Soc.* **83**, 2594 (1961).

⁵⁸ A. Wadsworth and M. C. Pangborn, *J. Biol. Chem.* **116**, 423 (1936).

⁵⁹ A. Homer, *Biochem. J.* **7**, 101 (1913).

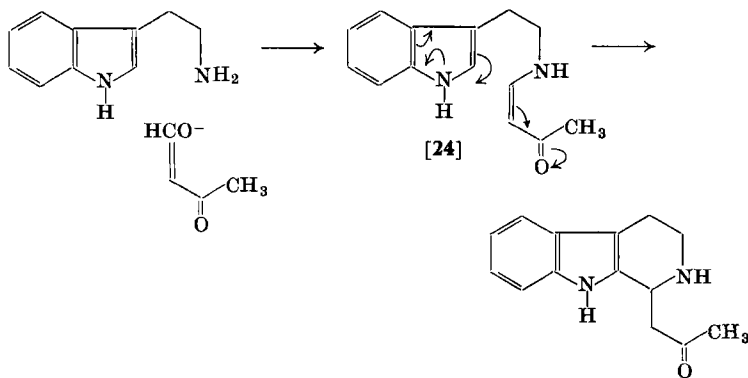
⁶⁰ J. C. Perrone, A. Iachan, and L. A. Moreira Carneiro, *Anais Acad. Brasil Cienc.* **25**, 107 (1953); *Chem. Abstr.* **49**, 231 (1955).

⁶¹ F. C. Uhle and L. S. Harris, *J. Am. Chem. Soc.* **79**, 102 (1957).

condensation of tryptophan with formaldehyde is the only instance in which a cyclized product may be obtained not only in the presence of acid³⁸ but also under alkaline conditions.^{40, 62, 63}

The intense blue color which is obtained when tryptophan, in the presence of an aldehyde, is treated with concentrated sulfuric acid containing an oxidizing agent (Adamkiewicz-Hopkins-Cole reaction) was believed to involve formation of a tetrahydro- β -carboline intermediate,⁴⁰ since most 1,2,3,4-tetrahydro- β -carboline derivatives yield a similar color with concentrated sulfuric acid containing an oxidizing agent. The two colors have now been shown to have different absorption spectra.⁶⁴ The nature of the "carboline-blue" color is still obscure.

Reaction of tryptamine with simple ketones has not been widely explored. Acetone in the presence of benzoyl chloride has been reported to yield 2-benzoyl-1,1-dimethyl-1,2,3,4-tetrahydro- β -carboline.⁶⁵ That the keto group is much less reactive than the aldehyde group is indicated by the fact that β -keto aldehydes, in the form of their acetals²⁷ or sodium salts, react with tryptamine at the aldehyde function to yield the conjugated enamine **24**, which undergoes ring closure *via* an intramolecular Michael addition.^{66, 67} The potentialities of this interesting modification of the Pictet-Spengler reaction have not yet been fully explored.



⁶² H. R. Snyder, H. G. Walker, and F. X. Werber, *J. Am. Chem. Soc.* **71**, 527 (1949).

⁶³ R. Speitel and E. Schlittler, *Helv. Chim. Acta* **32**, 860 (1949).

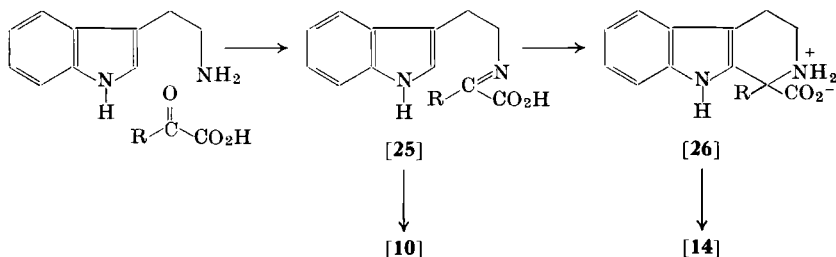
⁶⁴ C. H. Brieskorn and W. Reiners, *Ann. Chem.* **637**, 203 (1960).

⁶⁵ R. H. F. Manske, *Can. J. Research* **5**, 592 (1931).

⁶⁶ R. N. Schut, *Chem. Ind. (London)* 1246 (1960).

⁶⁷ R. N. Schut and W. G. Stryker, *Chem. Ind. (London)* 1308 (1961).

The reaction of tryptamine with α -oxo acids on the other hand has been extensively investigated by Hahn and his co-workers^{28, 68, 69} and represents an excellent route to the tetrahydro- β -carboline system, limited only by the availability of the acids. At moderate temperatures condensation of tryptamine hydrochloride with an enolizable α -keto acid in aqueous solution yields the corresponding 1,2,3,4-tetrahydro- β -carboline-1-carboxylic acid (**26**). Pyruvic acid,²⁸ phenylpyruvic acid and ring-substituted phenylpyruvic acids,^{28, 68, 69} α -ketoglutaric acid,^{69, 70} and glyoxylic acid^{71, 72} all yield the corresponding tetrahydro- β -carboline-1-carboxylic acid under mild conditions. These products can be decarboxylated by warming in alcoholic hydrogen chloride solution or in 12*N* hydrochloric acid to yield the corresponding 1-alkyl-1,2,3,4-tetrahydro- β -carboline.



Only in the case of the pyruvic acid condensation product was it possible to isolate the corresponding ethylester under these conditions. This, on mild hydrolysis, reverted to 1-methyl-1,2,3,4-tetrahydro- β -carboline-1-carboxylic acid, identical with the starting material, which therefore had the assigned structure **26** ($R = CH_3$) and was not the Schiff's base **25** ($R = CH_3$). Alkaline hydrolysis of the ester was accompanied by decarboxylation.⁶⁹

The decarboxylated products are obtained directly, however, if condensation of tryptamine with the α -oxo acid is carried out in aqueous solution at elevated temperature. This direct synthesis of a 1-substituted-1,2,3,4-tetrahydro- β -carboline has been carried out with

⁶⁸ G. Hahn and H. Werner, *Ann. Chem.* **520**, 123 (1935).

⁶⁹ G. Hahn and A. Hansel, *Ber.* **71**, 2163 (1938).

⁷⁰ S. Corsano and S. Algieri, *Ann. Chim. (Rome)* **50**, 75 (1960); *Chem. Abstr.* **55**, 27397 (1961).

⁷¹ Z. J. Vejdělek, V. Trčka, and M. Protiva, *J. Med. Pharm. Chem.* **3**, 427 (1961).

⁷² G. de Stevens, H. Lukaszewski, M. Sklar, A. Halamandaris, and H. M. Blatter, *J. Org. Chem.* **27**, 2457 (1962).

substituted phenylpyruvic acid derivatives^{29, 69, 73, 74, 75, 76, 77} and also with oxaloacetic acid and its monoethyl ester, carbethoxypyruvic acid,^{27, 78} α -ketoglutaric acid,^{70, 79} and a number of other α -oxo acids.^{27, 80} Even at low temperatures, α, α' -diketopimelic acid⁶⁹ and ethyl glyoxylate,⁸¹ the latter presumably after preliminary acid hydrolysis of the intermediate Schiff's base, gave the decarboxylated tetrahydro- β -carboline directly. An α -thioketo acid has also been used in the reaction.⁷⁷

It is improbable that the tetrahydro- β -carboline-1-carboxylic acid is an intermediate in the direct synthesis of the decarboxylated product. It is likely that at elevated temperature the α -keto acid Schiff's base **25** undergoes acid-catalyzed decarboxylation to the aldehyde Schiff's base **10**, which is then protonated and cyclizes in the normal manner. Primary amines are known to catalyze the otherwise difficult decarboxylation of α -keto acids to aldehydes.^{82, 83} At moderate temperature only is the acid-catalyzed cyclization of the keto acid Schiff's base **25** likely to be faster than its decarboxylation, and ring closure to the tetrahydro- β -carbolinecarboxylic acid can occur. Loss of a carboxyl group from this α -amino acid would not be expected to take place readily, since α -amino acids in general, including α -amino- α -phenylpropionic acid⁸⁴ which is analogous in structure to the carboline-1-carboxylic acids, do not decarboxylate but esterify in ethanolic hydrogen chloride. It is noteworthy that tetrahydroisoquinoline-1-carboxylic acids do not decarboxylate in the same manner as tetrahydro- β -carboline-1-carboxylic acids.⁸² A mechanism rationalizing the ease of decarboxylation of the latter compounds in strong acid is put forward in Section IV, B, 3.

⁷³ G. A. Swan, *J. Chem. Soc.* 1534 (1950).

⁷⁴ K. T. Potts and R. Robinson, *J. Chem. Soc.* 2675 (1955).

⁷⁵ W. Logemann, L. Almirante, L. Caprio, and A. Meli, *Chem. Ber.* **88**, 1952 (1955).

⁷⁶ W. Logemann, L. Caprio, L. Almirante, and A. Meli, *Chem. Ber.* **89**, 1043 (1956).

⁷⁷ A. Buzas, C. Hoffmann, and G. Regnier, *Bull. Soc. Chim. France* 645 (1960).

⁷⁸ G. B. Kline, *J. Am. Chem. Soc.* **81**, 2251 (1959).

⁷⁹ T. Wieland and E. Neeb, *Ann. Chem.* **600**, 161 (1956).

⁸⁰ S. Corsano and L. Panizzi, *Ann. Chim. (Rome)* **48**, 1025 (1958); *Chem. Abstr.* **53**, 10267 (1959).

⁸¹ M.-M. Janot, J. Keufer, and J. Le Men, *Bull. Soc. Chim. France* 230 (1952).

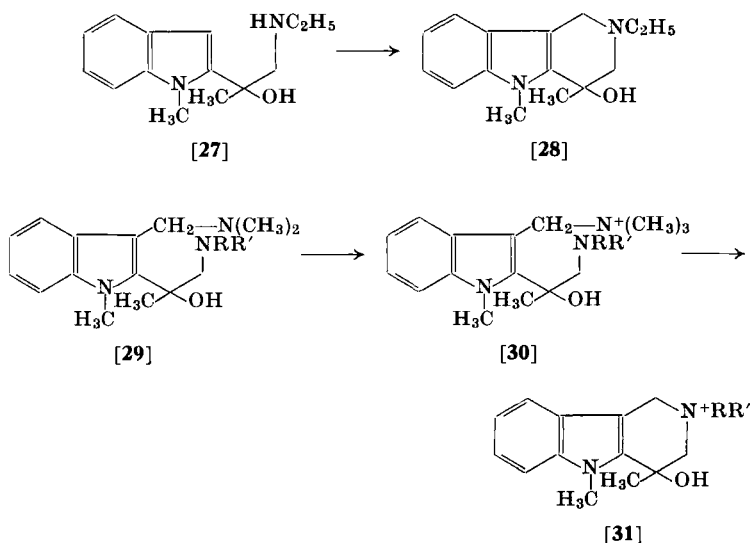
⁸² G. Hahn and K. Stiehl, *Ber.* **69**, 2627 (1936).

⁸³ W. Langenbeck, *Advan. Enzymol.* **14**, 163 (1953).

⁸⁴ A. McKenzie and J. R. Myles, *Ber.* **65**, 209 (1932).

Tryptophan condenses with α -oxo acids at room temperature to yield 1,2,3,4-tetrahydro- β -carboline-1,3-dicarboxylic acids. Both glyoxylic acid⁴⁰ and pyruvic acid⁸⁵ yield the expected products.

1,2,3,4-Tetrahydro- γ -carbolines may be prepared by an internal Mannich-type reaction between 2- β -aminoethylindoles and formaldehyde. Kehrle *et al.*⁸⁶ prepared **27** by the reaction of 2-lithio-1-methylindole with *N*-benzyl-*N*-ethylaminoacetone followed by debenzylation; treatment of **27** with formaldehyde led to the formation of the tetrahydro- γ -carboline **28**. Similarly, when the quaternary salts (**30**) of the Mannich bases (**29**) are heated at 100°, 1,2,3,4-tetrahydro- γ -carbolinium salts (**31**) are formed.



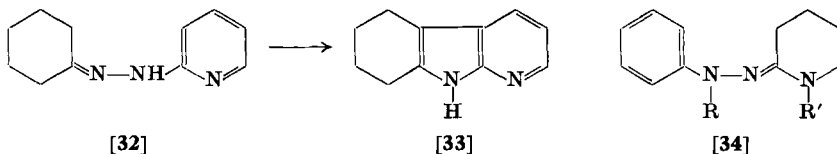
b. *The Fischer Cyclization.* The Fischer indole synthesis has proved to be a most versatile route to all the tetrahydrocarboline ring systems. The starting material may either be a piperidone phenylhydrazone, in which case the product is a 1,2,3,4-tetrahydrocarboline, or a cyclohexanone pyridylhydrazone, when a 5,6,7,8-tetrahydrocarboline is formed. More drastic conditions are generally required in the latter type of cyclization which involves ring closure onto a pyridine ring,

⁸⁵ R. Tschesche, H. Jenssen, and P. N. Rangachari, *Chem. Ber.* **91**, 1732 (1958).

⁸⁶ J. Kehrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta* **42**, 907 (1959).

and negative results have been reported in a number of attempted cyclizations using various 2-pyridyl- or 2-quinolyl-hydrazones,⁸⁷⁻⁹⁰

Okuda and Robison⁹⁰ effected the cyclization of cyclohexanone 2-pyridylhydrazone (**32**) to 5,6,7,8-tetrahydro- α -carboline (**33**) in 53% yield using polyphosphoric acid. 2-Oxopiperidine phenylhydrazone derivatives (**34**) (prepared from the phenylhydrazine and the 2-oxo-piperidine in the presence of phosphorus oxychloride) give 1,2,3,4-tetrahydro- α -carbolines.⁹¹



A variety of 1,2,3,4-tetrahydro- β -carbolines have been prepared from 3-piperidone phenylhydrazone derivatives. Used initially to obtain pentacyclic derivatives (**35**) related to the yohimbe alkaloids,^{73, 92, 93} this route was later extended to the synthesis of tetracyclic compounds (**36**).^{94, 95} 1-Methyl-5,6,7,8-tetrahydro- β -carboline (**37**) was prepared in low yield by heating cyclohexanone 2-methyl-3-pyridylhydrazone with zinc chloride,⁸⁹ a synthesis probably based on the similar preparation of the tetracyclic compound **38** starting from the corresponding quinolylhydrazine.⁹⁶ Abramovitch and Adams⁹⁷ extended this approach to the cyclization of cyclohexanone 3-pyridylhydrazone (**39**) itself. The main product was 6,7,8,9-tetrahydro- δ -carboline (**40**), a smaller amount of the β -isomer (**41**) also being obtained. This provides a convenient and readily reproducible route to the otherwise difficultly accessible δ -carboline ring system. The favored attack at carbon-2 over carbon-4 of the pyridine nucleus

⁸⁷ W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **103**, 1973 (1913).

⁸⁸ R. G. Fargher and R. Furness, *J. Chem. Soc.* **107**, 688 (1915).

⁸⁹ G. R. Clemo and R. J. W. Holt, *J. Chem. Soc.* **1313** (1953).

⁹⁰ S. Okuda and M. M. Robison, *J. Am. Chem. Soc.* **81**, 740 (1959).

⁹¹ H. Rapoport, D. S. Matteson, J. Gordon, and E. Coxworth, unpublished results. (Private communication from E.C.)

⁹² G. R. Clemo and G. A. Swan, *J. Chem. Soc.* **617** (1946).

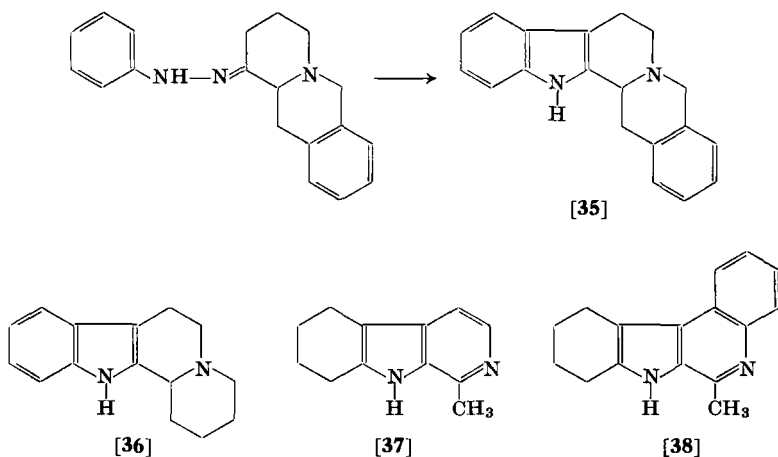
⁹³ R. T. Rapala, E. R. Lavagnino, E. R. Shepard, and E. Farkas, *J. Am. Chem. Soc.* **79**, 3770 (1957).

⁹⁴ W. A. Rechkow and D. S. Tarbell, *J. Am. Chem. Soc.* **74**, 4960 (1952).

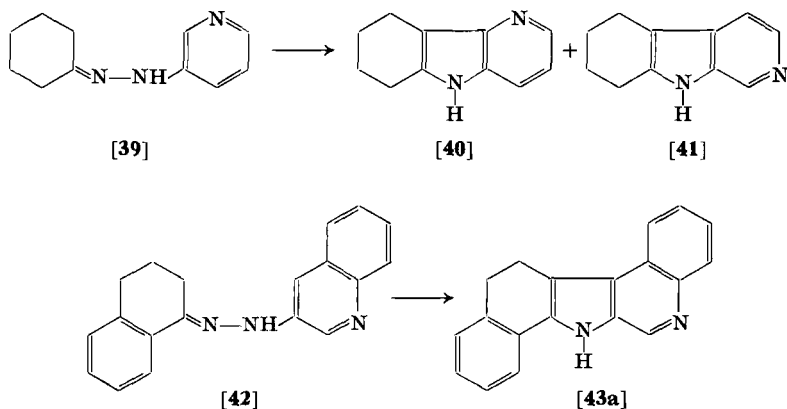
⁹⁵ J. Keufer, *Ann. Pharm. Franç.* **8**, 816 (1950); *Chem. Abstr.* **45**, 10246 (1951).

⁹⁶ G. M. Robinson and R. Robinson, *J. Chem. Soc.* **125**, 827 (1924).

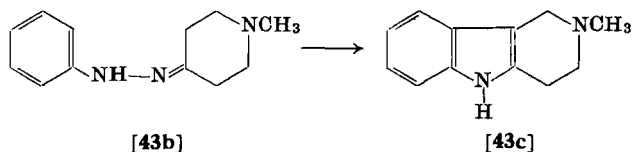
⁹⁷ R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.* **40**, 864 (1962).



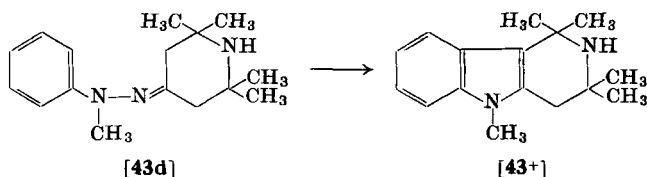
[contrast, for instance, the Graebe-Ullmann cyclization of 1- β -pyridylbenztriazole (Section III, E, 1, a)] has been discussed⁹⁷ in terms of the ground-state π -electron densities in pyridine derivatives. On the other hand,⁹⁸ heating the 3-quinolylylhydrazone (**42**) of α -tetralone with zinc chloride in *p*-cymene gave only one product, the structure of which was assumed to be 12,13-dihydro-7*H*-dibenz[*c, i*]- β -carboline (**43a**) by analogy with the cyclization of ethyl pyruvate 3-quinolylylhydrazone which gave 3*H*-pyrrolo[2,3-*c*]quinoline.



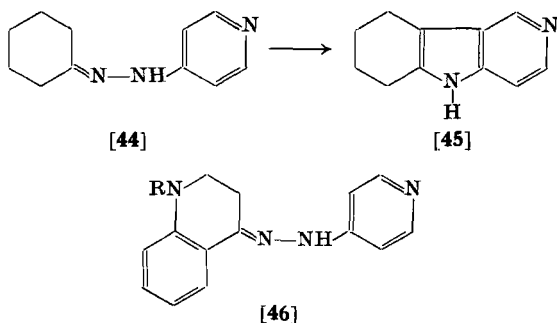
⁹⁸ T. R. Govindachari, S. Rajappa, and V. Sudarsanam, *Tetrahedron* **16**, 1 (1961).



Various substituted 1,2,3,4-tetrahydro- γ -carbolines (43c) may be obtained readily from 4-piperidone phenylhydrazones (43b).^{14, 21, 99-103} In fact, probably the first application of the Fischer cyclization to the synthesis of carbolines was introduced by Robinson



and Thornley¹⁰⁴ who obtained 1,1,3,3,5-pentamethyl-1,2,3,4-tetrahydro- γ -carboline (43e) from triacetoneamine phenylmethylhydrazone (43d). Again, the cyclization of cyclohexanone 4-pyridylhydrazones is more difficult than that of the phenylhydrazones. Thus, whereas cyclohexanone 4-pyridylhydrazone (44) is cyclized to 5,6,7,8-tetrahydro-



⁹⁹ A. H. Cook and K. J. Reid, *J. Chem. Soc.* 399 (1945).

¹⁰⁰ V. Rosnati and G. Palazzo, *Gazz. Chim. Ital.* **84**, 644 (1954).

¹⁰¹ N. F. Kucheroval and N. K. Kochetkov, *J. Gen. Chem. USSR (Eng. Transl.)* **26**, 3511 (1956).

¹⁰² N. K. Kochetkov, N. F. Kucheroval, L. P. Pronina, and M. I. Petruchenko, *J. Gen. Chem. USSR (Eng. Transl.)* **29**, 3581 (1959).

¹⁰³ A. N. Kost, L. G. Yudin, and S. A. Popravko, *Zh. Obshch. Khim.* **32**, 1544 (1962); *J. Gen. Chem. USSR (Eng. Transl.)* **32**, 1530 (1962).

¹⁰⁴ R. Robinson and S. Thornley, *J. Chem. Soc.* **125**, 2169 (1924).

γ -carboline (**45**) by heating with zinc chloride at 240° for 10 min, the cyclization of the 4-quinolone 4'-pyridylhydrazone (**46**) cannot be effected, the hydrazone being recovered either unreacted or partially decomposed.¹⁰⁵

c. *Intramolecular Enamine Addition.* A new approach to the synthesis of tetra- and penta-cyclic systems containing a 1,2,3,4-tetrahydro- β -carboline nucleus arose from the reinterpretation by Belleau¹⁰⁶ of the reductive cyclization of the 3-(*N*-ethylisoquinolyl)oxindole derivatives reported by Julian and Magnani.¹⁰⁷ The oxindoles **47** ($R = CH_3$) and **48** [the latter originally misformulated¹⁰⁷ as **47** ($R = CH_3$) with $>CH_2$ replacing $>CO$ in ring D] are converted by lithium aluminum hydride into the extended 1,2,3,4-tetrahydro- β -carboline system **49** ($R = CH_3$, $R' = R'' = H$). Belleau suggested that treatment of **48** with a limited amount of hydride would yield the corresponding 2-hydroxyindoline, which undergoes rearrangement to **49** ($R = CH_3$, $R' = R'' = H$). Belleau predicted that treatment with lithium aluminum hydride of the 3-(ethylisoquinolyl)indole derivative **50** would lead to **49** ($R = R' = R'' = H$) by way of the dihydro derivative **51**. This was confirmed by Potts and Robinson⁷⁴ and later applied to the synthesis of a number of substituted derivatives of **49** (e.g. $R = R' = H$, $R'' = CH_2OH$; $R = H$, $R' = CH_3O$, $R'' = CH_2OH$).^{108, 109} The use of sodium borohydride in place of lithium aluminum hydride did not lead to ring closure but to 3- $[\beta$ -(*N*-1,2,3,4-tetrahydroisoquinolyl)ethyl]indole derivatives (**53**).¹⁰⁹ Reductive cyclization by means of lithium aluminum hydride of the β -(3-indolyl)ethyl-1-isoquinoline (**52**) to the pentacyclic tetrahydro- β -carboline **49** ($R = R' = R'' = H$) has been reported. Strong acid alone sufficed to convert **52** into **54**, the oxo derivative of **49**.¹¹⁰

An extension of this synthetic route to tetracyclic systems of type **36** was described by Thesing and his co-workers,¹¹¹⁻¹¹³ who reduced the β -(3-indolyl)ethyl-1-pyridinium salt **55** ($R = H$) catalytically and

¹⁰⁵ F. G. Mann, A. F. Prior, and T. J. Wilcox, *J. Chem. Soc.* 3830 (1959).

¹⁰⁶ B. Belleau, *Chem. Ind. (London)* 229 (1955).

¹⁰⁷ P. L. Julian and A. Magnani, *J. Am. Chem. Soc.* **71**, 3207 (1949).

¹⁰⁸ R. C. Elderfield and B. A. Fischer, *J. Org. Chem.* **23**, 332 (1958).

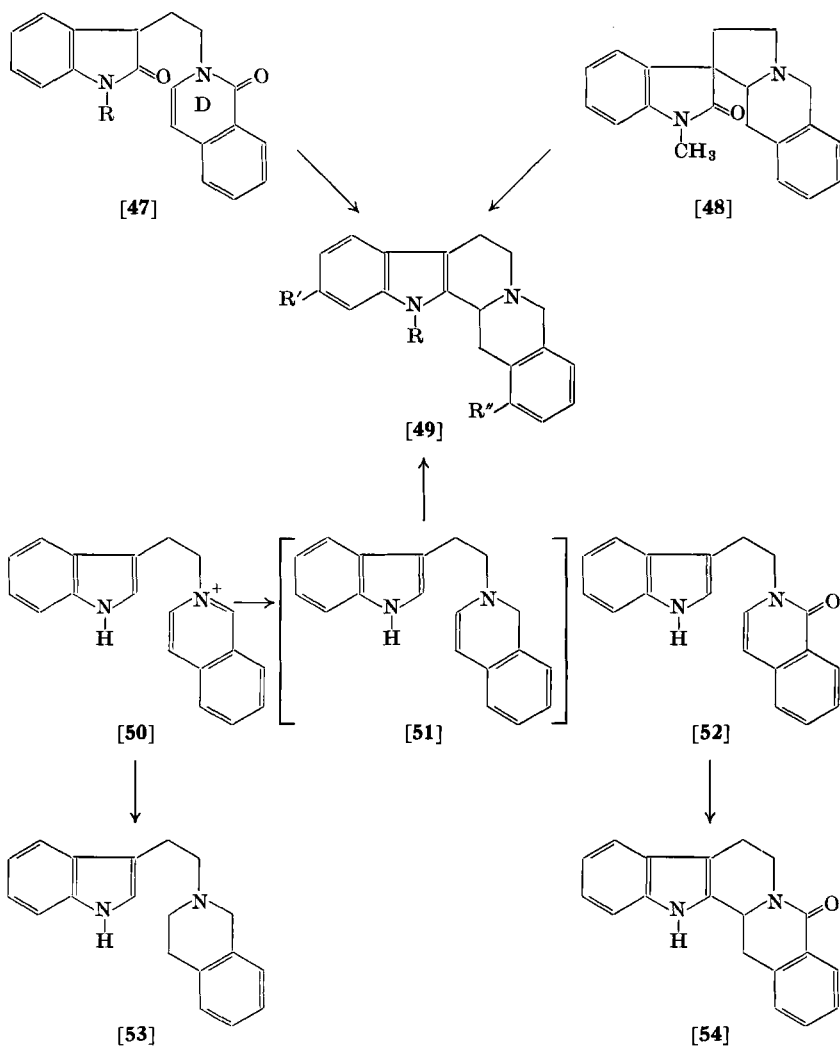
¹⁰⁹ R. C. Elderfield and B. A. Fischer, *J. Org. Chem.* **23**, 949 (1958).

¹¹⁰ C. Ribbens and W. T. Nauta, *Rec. Trav. Chim.* **79**, 854 (1960).

¹¹¹ J. Thesing, H. Ramloch, C. H. Willersinn, and F. Funk, *Angew. Chem.* **68**, 387 (1956).

¹¹² J. Thesing, H. Ramloch, and C. H. Willersinn, *Chem. Ber.* **89**, 2896 (1956).

¹¹³ J. Thesing and W. Festag, *Experientia* **15**, 127 (1959).

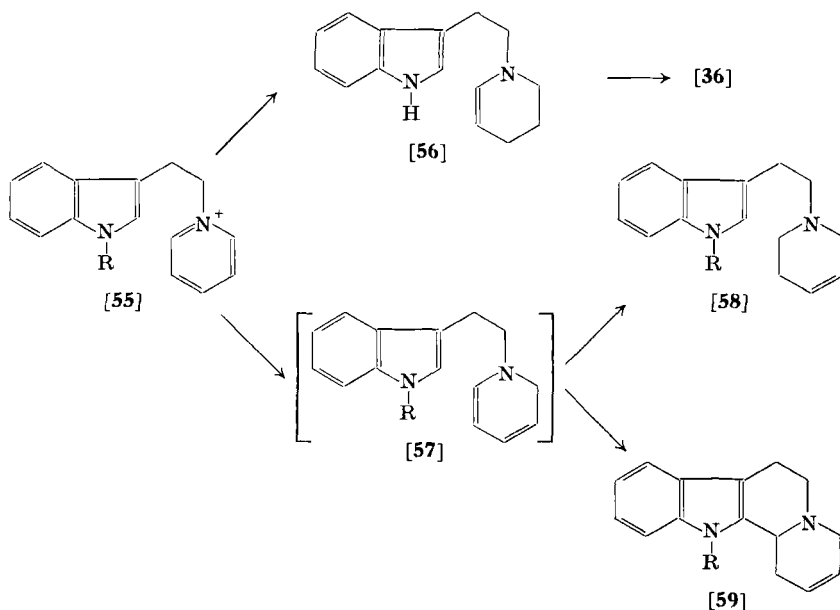


obtained the intermediate **56** which, in the presence of acid, underwent cyclization to the 1,2,3,4-tetrahydro- β -carboline derivative **36**.

The salt **55** ($R = H$) did not cyclize on reduction with metal hydrides, but instead yielded the tryptamine derivative **58** ($R = H$) as the sole ¹¹⁴

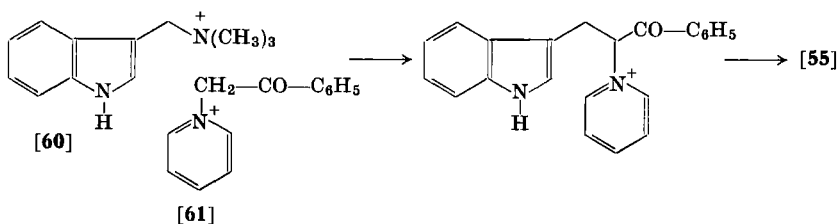
¹¹⁴ R. C. Elderfield, B. A. Fischer, and J. M. Lagowski, *J. Org. Chem.* **22**, 1376 (1957).

or major¹¹⁵ product. This anomaly was clarified by Wenkert's group.¹¹⁵ They postulated that the hydride, acting as a base, abstracted the *ind-N* proton to form an indole-aluminumhydride complex, the Al-H atoms of which were responsible for an intramolecular reduction of the enamine **57**, the obligatory intermediate in the cyclization reaction, and therefore for the failure of the ring closure. In accord with this view it was shown that lithium aluminum hydride

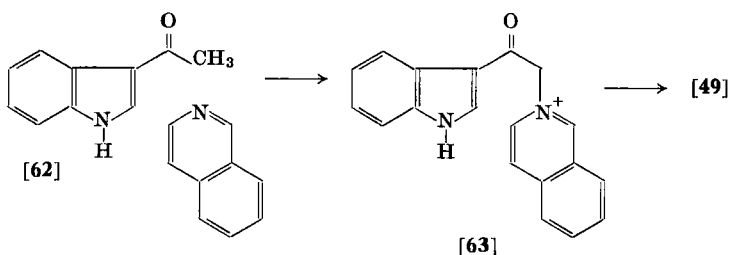


reduction of the *ind-N*-substituted salt **55** ($R = CH_3$) gave the cyclized compound **59** ($R = CH_3$) as the sole product and that reduction of **55** ($R = H$) with lithium tri-*t*-butoxyaluminum hydride, whose complex with the *ind-N* possesses no Al-H bonds and therefore no reducing power, yields the cyclized compound (**59**; $R = H$) as the major product. In addition to the major route of access to the starting materials **50** and **55** [i.e., quaternization of pyridine or isoquinoline with β -(3-indolyl)-ethyl bromide],^{109, 114, 115} two elegant procedures have recently been described. In the first, the reaction of gramine methiodide (**60**) with the quaternary pyridinium salt **61** leads to the desired product (**55**) in

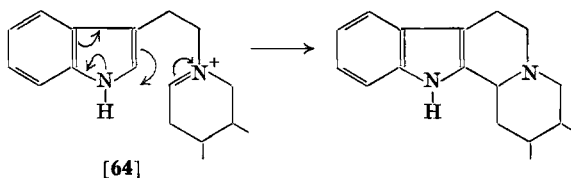
¹¹⁵ E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.* **84**, 3732 (1962).



two steps.¹¹² The other method involves the iodine-catalyzed quaterization of isoquinoline by 3-acetylindole (62) to give 63, which is cyclized to 49 by lithium aluminum hydride.¹¹⁶



There can be little doubt that the crucial, acid-catalyzed step in these cyclization reactions, analogous to that in the Pictet-Spengler type ring closure, involves the charged species 64 (cf. 11).

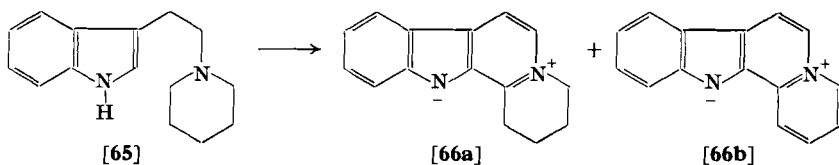


In a recent variation of this synthesis of the tetrahydro- β -carboline system, hexahydro derivatives (65) of the salt 55 were cyclized to fully aromatic β -carboline derivatives (66a and 66b) on palladium dehydrogenation, presumably by way of an enamine intermediate.¹¹⁷

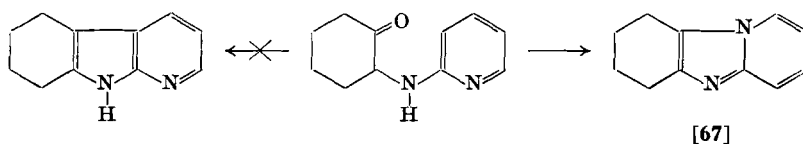
d. *Syntheses from Cyclohexanone Derivatives.* A German Patent claimed that 5,6,7,8-tetrahydro- α -carboline was formed in the reaction

¹¹⁶ D. R. Liljgren and K. T. Potts, *Proc. Chem. Soc.* 340 (1960); *J. Org. Chem.* **27**, 377 (1962).

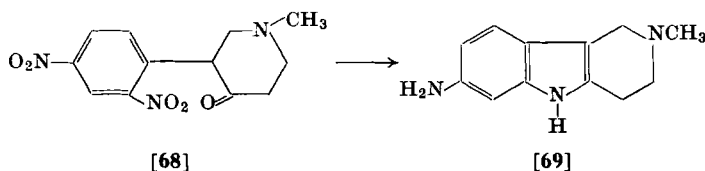
¹¹⁷ E. Wenkert and J. Kilzer, *J. Org. Chem.* **27**, 2283 (1962).



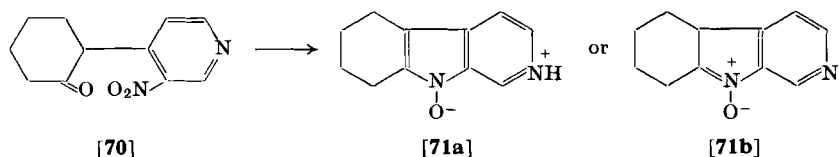
of 2-chlorocyclohexanone with 2-aminopyridine in the presence of sodamide.¹¹⁸ This was later shown to be incorrect. The product was actually 4,5,6,7-tetrahydropyrido[1,2-*a*]benzimidazole (67).¹¹⁹



Tetrahydrocarboline derivatives have recently been synthesized from 2-*o*-nitroarylated cyclohexanone derivatives.¹²⁰ Thus, reductive cyclization of 3-(2,4-dinitrophenyl)-1-methyl-4-piperidone (68) (prepared by the reaction of 2,4-dinitrochlorobenzene with 1-methyl-4-*N*-pyrrolidino-3-piperidine) gave 7-amino-2-methyl-1,2,3,4-tetrahydro- γ -carboline (69). Neither catalytic nor chemical reduction of the



2-(3'-nitro-4'-pyridyl)cyclohexanone 70 proceeded beyond the hydroxylamine stage, cyclization apparently leading to an amphoteric polar compound formulated either as the inner salt 71a or as the



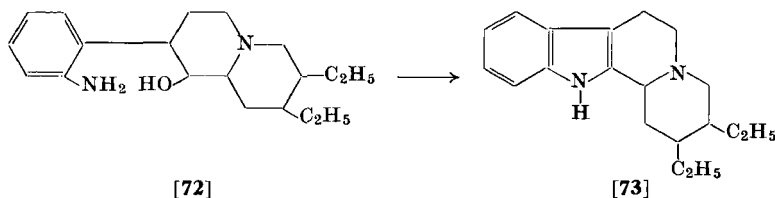
¹¹⁸ J. Reitmann, German Patent 547,985 (1930); *Chem. Abstr.* **26**, 3514 (1932).

¹¹⁹ N. Campbell and E. B. McCall, *J. Chem. Soc.* 2411 (1951).

¹²⁰ M. E. Kuehne, *J. Am. Chem. Soc.* **84**, 837 (1962).

imine oxide (**71b**). The method should be amenable to extension to the synthesis of δ -carboline derivatives, starting from the readily available 2-chloro-3-nitropyridine.

A synthesis of an extended 1,2,3,4-tetrahydro- β -carboline system (**73**) is somewhat similar. The 4-*o*-aminophenyl-3-piperidinol derivative **72**, obtained in several steps from cinchonine, undergoes



Oppenauer oxidation and spontaneous cyclization to give **73**.¹²¹ This represents an interesting chemical route from the cinchona to the indole alkaloids.

2. From Other Oxidation States of the Preformed Ring System

a. *Tetrahydrocarbolines from Carbolines.* (i) *1,2,3,4-Tetrahydrocarbolines.* The reduction of the carbolines to the tetrahydro stage has received considerable attention. Sodium and various alcohols have often been used for this purpose and, as expected on the basis of its susceptibility to attack by nucleophilic reagents, the pyridine ring is the one which is reduced. Sodium and ethanol,¹²²⁻¹²⁷ *n*-butanol,^{14, 43} and amyl¹²⁸ and *iso*amyl alcohol^{77, 81} have been used with success to reduce β -carboline derivatives to the corresponding 1,2,3,4-tetrahydro- β -carbolines. Reduction of *pyr-N*-quaternary β -carbolinium

¹²¹ E. Ochiai and M. Ishikawa, *Tetrahedron* **7**, 228 (1959).

¹²² O. Fischer, *Ber.* **22**, 637 (1889).

¹²³ Y. Asahina, T. Irie, and T. Ohta, *J. Pharm. Soc. Japan.* **47**, 541 (1927); *Chem. Abstr.* **21**, 3622 (1927).

¹²⁴ G. P. Men'shikov, E. L. Gurevich, and G. A. Samsonova, *J. Gen. Chem. USSR (Eng. Transl.)* **20**, 1995 (1950).

¹²⁵ T. F. Platonova, A. D. Kuzovkov, and P. S. Massagetov, *J. Gen. Chem. USSR (Eng. Transl.)* **26**, 3593 (1956).

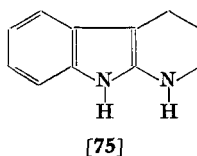
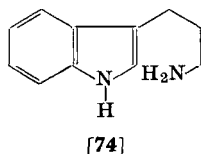
¹²⁶ N. I. Koretskaya, A. V. Danilova, and L. M. Utkin, *J. Gen. Chem. USSR (Eng. Transl.)* **27**, 611 (1957).

¹²⁷ S. G. Agbalyan, *Izv. Akad. Nauk Arm. SSR Khim. Nauki.* **14**, 277 (1961); *Chem. Abstr.* **56**, 8695 (1962).

¹²⁸ J. Keufer, *Bull. Soc. Chim. France* 109 (1950).

salts under these conditions either gives poor yields^{129, 130} or fails completely.¹²⁶ Smooth reduction of these quaternary salts to *pyr-N*-alkyl-1,2,3,4-tetrahydro- β -carboline derivatives can be accomplished with sodium borohydride in methanol solution.^{6, 43, 79, 131-134} The anhydro-bases derived from these quaternary salts are reported to be stable to sodium borohydride.⁶

The reduction of α -carboline is not straightforward. Lawson *et al.*¹³⁵ found that reduction of α -carboline with sodium in boiling *iso*amyl alcohol yielded unidentified products which gave a magenta coloration with Ehrlich's reagent. The color was not discharged on cooling the solution. Freak and Robinson¹³⁶ repeated the reduction using *n*-butanol instead of *iso*amyl alcohol and obtained what was clearly a mixture of products, one of which was shown to be 3- γ -aminopropylindole (74) since it gave the known phthalimido derivative of this



primary amine. On the other hand, Witkop⁶ obtained a low yield of a crystalline material, m.p. 82–83°, from the sodium–butanol reduction. This substance gave a dark-red color when it was warmed with Ehrlich's reagent, but the color disappeared when the solution was cooled. Since this compound was different from the known¹³⁷ 3- γ -aminopropylindole and because it exhibited one strong NH band at

¹²⁹ W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **121**, 1872 (1922).

¹³⁰ H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951).

¹³¹ M. V. Rubtsov, L. N. Yakhontov, and D. M. Krasnokutskaya, *J. Gen. Chem. USSR (Eng. Transl.)* **29**, 3232 (1959).

¹³² L. N. Yakhontov and M. V. Rubtsov, *J. Gen. Chem. USSR (Eng. Transl.)* **28**, 3139 (1958).

¹³³ L. N. Yakhontov and M. V. Rubtsov, *J. Gen. Chem. USSR (Eng. Transl.)* **29**, 1172 (1959).

¹³⁴ C. F. Huebner, H. A. Troxell, and D. C. Schroeder, *J. Am. Chem. Soc.* **75**, 5887 (1953).

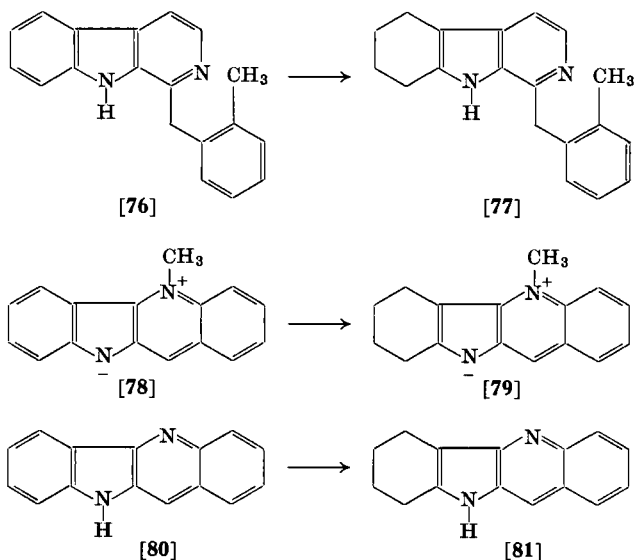
¹³⁵ W. Lawson, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **125**, 626 (1924).

¹³⁶ R. H. Freak and R. Robinson, *J. Chem. Soc.* 2013 (1938).

¹³⁷ R. Majima and T. Hoshino, *Ber.* **58**, 2046 (1925).

3497 cm^{-1} in the infrared region of the spectrum but no such bands between 1667 and 1481 cm^{-1} , Witkop concluded that the reduction product was actually 1,2,3,4-tetrahydro- α -carboline (75). A quaternary α -carbolinium salt, 1,9-dimethyl- α -carbolinium iodide, has been reduced with sodium borohydride to what was believed to be the corresponding 1,2,3,4-tetrahydro- α -carboline.⁶ The reduction of γ -carboline to 1,2,3,4-tetrahydro- γ -carboline with sodium and butanol takes place readily,¹⁰⁴ whereas no pure product was obtained when δ -carboline was similarly reduced though the resultant mixture did give a positive Ehrlich reaction.⁹⁷

Anhydro-bases derived from quaternary β -carbolinium salts are reduced to *pyr-N*-substituted-1,2,3,4-tetrahydro- β -carboline derivatives on hydrogenation over Adams' catalyst in methanol solution made alkaline to ensure the presence of anhydro-base.^{27, 43, 138-142} The quaternary salts themselves, or *pyr-N*-unsubstituted β -carbolines, are stable to hydrogenation under these conditions.



¹³⁸ P. Karrer and P. Waser, *Helv. Chim. Acta.* **32**, 409 (1949).

¹³⁹ M.-M. Janot, R. Goutarel, A. Le Hir, M. Amin, and V. Prelog, *Bull. Soc. Chim. France* 1085 (1952).

¹⁴⁰ A. Le Hir, R. Goutarel, and M.-M. Janot, *Bull. Soc. Chim. France* 1091 (1952).

¹⁴¹ A. Le Hir, M.-M. Janot, and R. Goutarel, *Bull. Soc. Chim. France* 1027 (1953).

¹⁴² N. A. Hughes and H. Rapoport, *J. Am. Chem. Soc.* **80**, 1604 (1958).

(ii) *5,6,7,8-Tetrahydrocarbolines*. Hydrogenation of β -carbolines over platinum oxide in glacial acetic acid takes a course different from that observed under weakly basic conditions. Two molar equivalents of hydrogen are slowly taken up and the product is the 5,6,7,8-tetrahydro derivative.^{81, 130, 138, 142} Reduction of yobyrine (**76**) in this way gives rise to the tetrahydroyobyrine **77**.¹³⁸ Similarly, reduction of cryptolepine (**78**) or of quindoline (**80**) gives the corresponding benz-tetrahydro compounds **79** and **81**, respectively.¹⁴³

b. *1,2,3,4-Tetrahydro- β -carbolines from 3,4-Dihydro- β -carbolines*. A variety of reagents have been used in the reduction of 3,4-dihydro- β -carbolines to the corresponding 1,2,3,4-tetrahydro derivatives. Sodium and ethanol^{13, 20, 92, 122, 144, 145} or amyl and isoamyl alcohol,^{146, 147, 148} zinc and hydrochloric¹²² or acetic acid,¹⁴⁹ and sodium amalgam in acid solution¹⁵⁰ have been used in the chemical reduction of 3,4-dihydro- β -carbolines; palladium¹⁵¹ or platinum oxide^{134, 152} have been used to effect the corresponding reduction catalytically. Quaternary 3,4-dihydro- β -carbolinium salts have been reduced to 2-alkyl-1,2,3,4-tetrahydro- β -carbolines with sodium borohydride,^{134, 153} but an abnormal product was obtained from harmaline methochloride.¹⁵³

A large number of compounds containing an extended 3,4-dihydro- β -carbolinium system (**82**) have been converted similarly into the corresponding tetrahydro- β -carboline derivatives (**83a** and **83b**). In many cases the reaction is stereospecific and one or the other of the epimers **83a** and **83b** has been isolated as the sole or major product. Sodium and ethanol^{154, 155}; tin and hydrochloric acid¹⁵⁵; zinc and

¹⁴³ E. Gellert, Raymond-Hamet, and E. Schlittler, *Helv. Chim. Acta* **34**, 642 (1951).

¹⁴⁴ Y. Asahina and S. Osada, *J. Pharm. Soc. Japan* **46**, 629 (1926).

¹⁴⁵ G. Hahn and H. F. Gudjons, *Ber.* **71**, 2175 (1938).

¹⁴⁶ O. Fischer, *Ber.* **30**, 2481 (1897).

¹⁴⁷ O. Fischer, *Ber.* **47**, 99 (1914).

¹⁴⁸ A. Buzas and G. Regnier, *Bull. Soc. Chim. France* 1589 (1960).

¹⁴⁹ M. Onda and M. Kawanishi, *J. Pharm. Soc. Japan* **76**, 966 (1956); *Chem. Abstr.* **51**, 2824 (1957).

¹⁵⁰ W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **115**, 933 (1919).

¹⁵¹ H. Nishikawa, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **125**, 657 (1924).

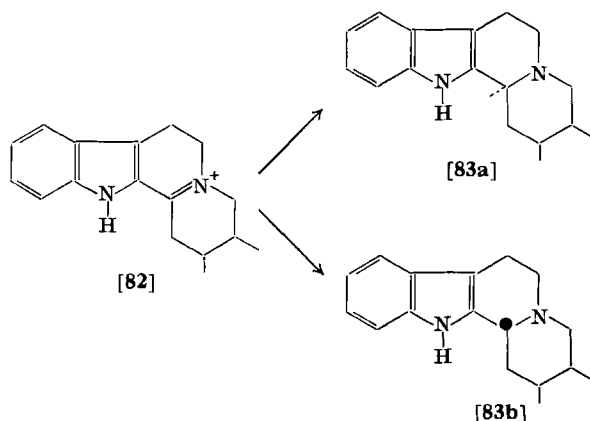
¹⁵² M. Onda and M. Sasamoto, *Pharm. Bull. (Tokyo)* **5**, 305 (1957); *Chem. Abstr.* **52**, 14631 (1958).

¹⁵³ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **75**, 4474 (1953).

¹⁵⁴ G. Stork and R. K. Hill, *J. Am. Chem. Soc.* **76**, 949 (1954).

¹⁵⁵ G. Stork and R. K. Hill, *J. Am. Chem. Soc.* **79**, 495 (1957).

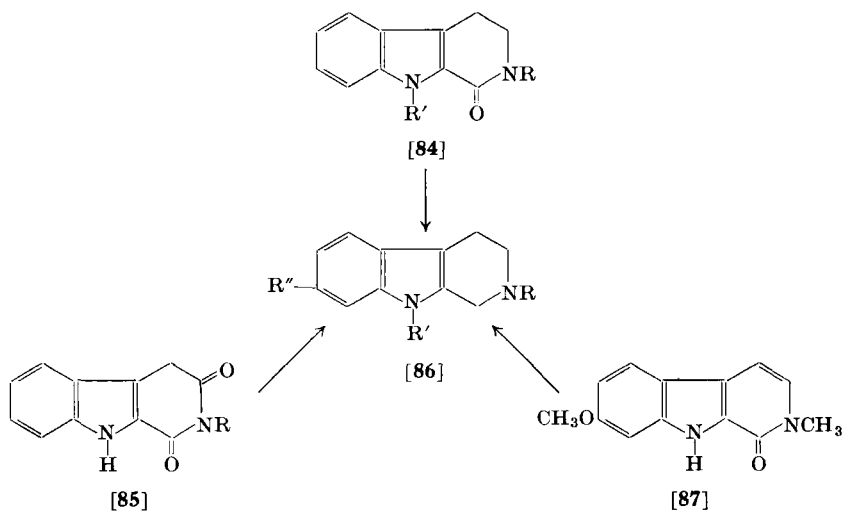
hydrochloric, perchloric, or acetic acid¹⁵⁶⁻¹⁶¹; sodium borohydride^{34, 121, 157, 160-163}; and hydrogen over platinum oxide^{57, 74, 154, 155, 157, 164-170} have been used in the reaction.



c. *1,2,3,4-Tetrahydro-β-carbolines from Oxo-β-carbolines.* 1,2,3,4-Tetrahydro-1-oxo-β-carbolines (**84**) are convenient starting materials for the synthesis of 1,2,3,4-tetrahydro-β-carbolines (**86**). 1,2,3,4-Tetrahydro-1-oxo-β-carboline and its 7-methoxy-2-methyl derivative were

- ¹⁵⁶ F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.* **78**, 2022 (1956).
- ¹⁵⁷ W. O. Godtfredson and S. Vangedal, *Acta Chem. Scand.* **10**, 1414 (1956).
- ¹⁵⁸ L. Velluz, G. Muller, R. Joly, G. Nominé, J. Mathieu, A. Allais, J. Warnant, J. Valls, R. Bucourt, and J. Jolly, *Bull. Soc. Chim. France* 673 (1958).
- ¹⁵⁹ M. Protiva, M. Rajšner, and J. O. Jílek, *Monatsh. Chem.* **91**, 703 (1960); L. Novák and M. Protiva, *Collection Czech. Chem. Commun.* **26**, 681 (1961).
- ¹⁶⁰ L. Bláha, J. Weichet, J. Žváček, S. Šmolík, and B. Kakáč, *Collection Czech. Chem. Commun.* **25**, 237 (1960).
- ¹⁶¹ L. Bláha, B. Kakáč, and J. Weichet, *Collection Czech. Chem. Commun.* **27**, 857 (1962).
- ¹⁶² E. Wenkert and D. K. Roychaudhuri, *J. Org. Chem.* **21**, 1315 (1956).
- ¹⁶³ E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.* **80**, 1613 (1958).
- ¹⁶⁴ F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.* **78**, 2021 (1956).
- ¹⁶⁵ E. E. van Tamelen and M. Shamma, *J. Am. Chem. Soc.* **76**, 950 (1954).
- ¹⁶⁶ E. E. van Tamelen, P. E. Aldrich, and T. J. Katz, *J. Am. Chem. Soc.* **79**, 6426 (1957).
- ¹⁶⁷ S. Sugawara and Y. Deguchi, *Chem. Pharm. Bull. (Tokyo)* **8**, 879 (1960); *Chem. Abstr.* **55**, 24746 (1961).
- ¹⁶⁸ S. Sugawara, M. Terashima, and Y. Kanaoka, *Pharm. Bull. (Tokyo)* **4**, 16 (1956); *Chem. Abstr.* **51**, 3593 (1957).
- ¹⁶⁹ Y. Ban and M. Seo, *Chem. Ind. (London)* 235 (1960).
- ¹⁷⁰ Y. Ban and M. Seo, *Tetrahedron* **16**, 5 (1961).

reduced with sodium and *n*-butanol.^{129, 171} Substitution of propanol for butanol did not lead to an increased yield. This method was extended to the preparation of other substituted 1,2,3,4-tetrahydro- β -carbolines.^{172, 173} Attempts to reduce the amide linkage in 1,2,3,4-tetrahydro-1-oxo- β -carbolines¹⁷² and in their *ind-N*-methyl derivatives¹⁷³ with lithium aluminum hydride in ether or tetrahydrofuran solution failed, probably due to the formation of an insoluble complex (with the amide-NH) before reduction. On the other hand, the 2,9-dimethyl derivatives were readily reduced under these conditions. More recently it has been found that even the unmethylated compounds can be reduced in high yield with lithium aluminum hydride in boiling dioxane¹⁷⁴ and that 2-acyl-1,2,3,4-tetrahydro-1-oxo- β -carbolines yield the corresponding 2-alkyl analogs on reduction with lithium aluminum hydride in ether.¹⁷⁵



Other oxo- β -carbolines which have been converted into 1,2,3,4-tetrahydro- β -carbolines are 2-benzyl-1,2,3,4-tetrahydro-1,3-dioxo- β -carboline (**85**; $R = \text{CH}_2\text{C}_6\text{H}_5$), which was reduced to 2-benzyl-1,2,3,4-

¹⁷¹ J. N. Ashley and R. Robinson, *J. Chem. Soc.* 1376 (1928).

¹⁷² R. A. Abramovitch and D. Shapiro, *J. Chem. Soc.* 4589 (1956).

¹⁷³ R. A. Abramovitch, *J. Chem. Soc.* 4593 (1956).

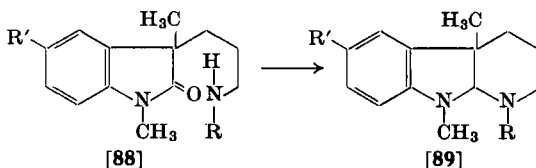
¹⁷⁴ G. Frangatos, G. Kohan, and F. L. Chubb, *Can. J. Chem.* **38**, 1082 (1960).

¹⁷⁵ I. J. Pachter, R. J. Mohrbacher, and D. E. Zacharias, *J. Am. Chem. Soc.* **83**, 635 (1961).

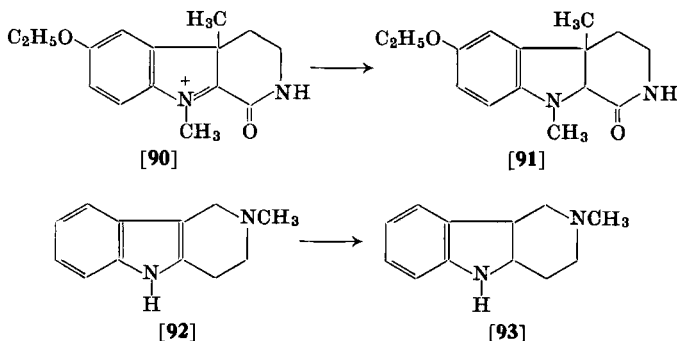
tetrahydro- β -carboline (**86**; $R' = R'' = H$, $R = CH_2C_6H_5$) by means of lithium aluminum hydride,¹⁵² and a number of 1,2-dihydro-1-oxo- β -carboline derivatives (e.g. **87**), which yielded the tetrahydro products on reduction with sodium in butanol.^{25, 129}

B. HEXAHYDROCARBOLINES

The hexahydro- β -carboline ring system occurs in nature in a number of alkaloids, e.g. ajmaline. A synthesis of 2,2,4a-trimethyl-1,2,3,4,4a,9a-hexahydro- β -carbolinium chloride has been mentioned, but no details have been given.¹⁷⁶



Homoesermetol (1,4a,9-trimethyl-6-methoxy-1,2,3,4,4a,9a-hexahydro- α -carboline (**89**; $R = CH_3$, $R' = OCH_3$) may be prepared in a manner analogous to that used for the preparation of eseroline. Thus, when the 3- γ -oxindolylpropylamine **88** ($R = CH_3$, $R' = OCH_3$) is reduced with sodium in butanol, homoermetol is obtained.¹⁷⁷ Reductive cyclization of **88** ($R = R' = H$) with lithium aluminum hydride has recently been reported.¹⁷⁸



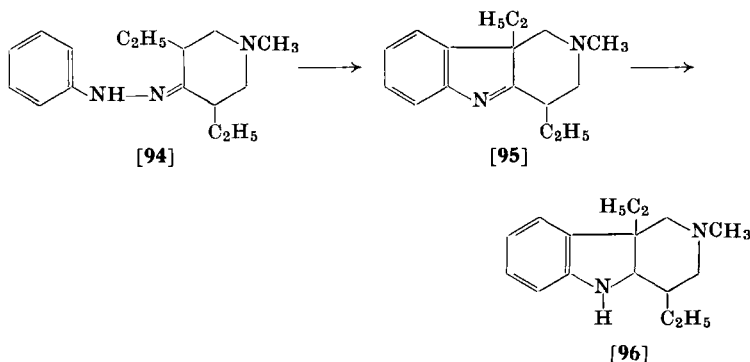
¹⁷⁶ A. R. Battersby and H. F. Hodson, *J. Chem. Soc.* 736 (1960).

¹⁷⁷ M. N. Kolosov, L. I. Metreveli, and N. A. Preobrazhenskii, *J. Gen. Chem. USSR (Eng. Transl.)* **23**, 2143 (1953).

¹⁷⁸ T. Hino, *Chem. Pharm. Bull. (Tokyo)* **9**, 988 (1962), footnote p. 991.

4a,9-Dimethyl-6-ethoxy-1,2,3,4,4a,9a-hexahydro-1-oxo- β -carboline (**91**) was obtained by the zinc and hydrochloric acid reduction of **90**.¹⁷⁹

The reduction of 2-methyl-1,2,3,4-tetrahydro- γ -carboline (**92**) with zinc and hydrochloric acid in the presence of mercuric chloride gives the indolenine derivative, 2-methyl-1,2,3,4,4a,9b-hexahydro- γ -carboline (**93**).¹⁸⁰ A related compound, 4,9b-diethyl-2-methyl-1,2,3,4,4a,9b-hexahydro- γ -carboline (**96**), was obtained by catalytic hydrogenation of **95**, which was prepared by Fischer ring closure of the phenylhydrazine **94**.¹⁰⁰ The stereochemistry of the B/C ring junction in these hexahydrocarbolines has not been investigated.



C. DIHYDROCARBOLINES

1. From Non-Carboline Precursors

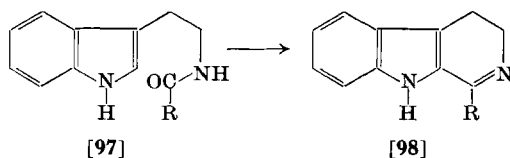
a. *The Bischler-Napieralski Reaction.* A versatile and widely applied reaction leading to 3,4-dihydro- β -carboline derivatives is an adaptation of the Bischler-Napieralski synthesis of 3,4-dihydroisoquinolines.¹¹ Introduced by Asahina and Osada¹⁴⁴ and extended by Späth and Lederer,^{53, 181} the reaction consists of the cyclodehydration of an *N* β -acyltryptamine derivative (**97**) by means of phosphorus pentoxide, phosphorus oxychloride, or polyphosphoric acid to yield the corresponding 1-substituted-3,4-dihydro- β -carboline (**98**).

The work carried out before 1950 has been exhaustively reviewed.¹¹ Only special aspects and recent developments will be discussed here.

¹⁷⁹ R. Robinson and H. Suginome, *J. Chem. Soc.* 304 (1932).

¹⁸⁰ N. K. Kochetkov, N. F. Kucherova, and I. G. Zhukova, *J. Gen. Chem. USSR (Eng. Transl.)* **31**, 853 (1961).

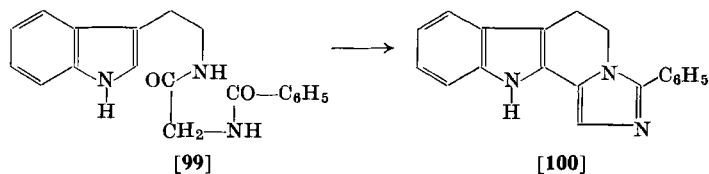
¹⁸¹ E. Späth and E. Lederer, *Ber.* **63**, 120 (1930).



Amides, prepared by condensation of tryptamine or substituted tryptamines with a large number of aliphatic,^{15, 53, 145, 181-183a} homocyclic,^{184, 185} aromatic,^{13, 20, 65, 92, 134, 144, 148, 149, 186, 187} and heterocyclic^{188, 189} acids, have been used in the reaction. In few cases only did ring closure fail.^{13, 188, 190}

3,4-Dihydro- β -carboline itself, the parent compound of the group, whose original preparation from $N\beta$ -formyltryptamine was doubtful,⁵³ has now been described^{162, 191} and characterized.¹⁹² Its 9-methyl⁵ and 6-methoxy¹⁷⁵ derivatives have also been prepared.

Emphasis in recent applications of the method has been placed on the synthesis of tetra- and penta-cyclic structures containing a dihydro- β -carboline system or its equivalent. Thus the tetracyclic system **100** was obtained from the amide (99) of tryptamine and hippuric acid.¹⁹³



¹⁸² E. Hardegger and H. Corrodi, *Helv. Chim. Acta* **39**, 984 (1956).

¹⁸³ L. Dúbravková, I. Ježo, P. Šefčovič, and Z. Votický, *Chem. Zvesti* **13**, 16 (1959).

^{183a} M. F. Petrova, N. S. Kaverina, and G. P. Men'shikov, *Zh. Obshch. Khim.* **33**, 1333 (1963); *Chem. Abstr.* **59**, 10149 (1963).

¹⁸⁴ Y.-S. Kao and R. Robinson, *J. Chem. Soc.* 2865 (1955).

¹⁸⁵ M. Protiva, J. O. Jilek, V. Hach, E. Adlerová, and V. Mychajlyszyn, *Collection Czech. Chem. Commun.* **24**, 83 (1959).

¹⁸⁶ P. L. Julian, W. J. Karpel, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.* **70**, 180 (1948).

¹⁸⁷ H. R. Snyder and L. Katz, *J. Am. Chem. Soc.* **69**, 3140 (1947).

¹⁸⁸ L. Marion, R. H. F. Manske, and M. Kulka, *Can. J. Research* **24B**, 224 (1946).

¹⁸⁹ A. R. Battersby, G. C. Davidson, and J. C. Turner, *J. Chem. Soc.* 3899 (1961).

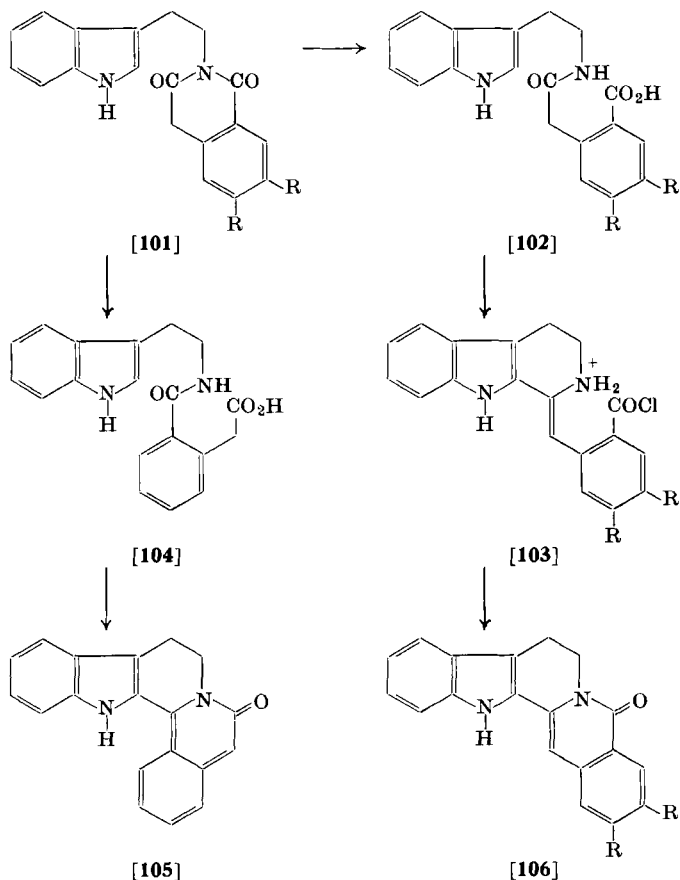
¹⁹⁰ G. A. Swan, *J. Chem. Soc.* 1720 (1949).

¹⁹¹ C. Schöpf and H. Steuer, *Ann. Chem.* **558**, 124 (1947).

¹⁹² R. N. Gupta and I. D. Spenser, *Can. J. Chem.* **40**, 2049 (1962).

¹⁹³ I. W. Elliott, *J. Org. Chem.* **27**, 3302 (1962).

The first direct approach to a pentacyclic system, based on the condensation product **101** of tryptamine with a homophthalic acid or anhydride, was introduced by Clemo and Swan^{92, 194} and extended to reduced and substituted homophthalates.^{73, 195-198} Esterification of the homophthalamic acid **102** (R = H) and ring closure with phosphorus oxychloride yielded the carboline derivative **106** (R = H). The



¹⁹⁴ G. R. Clemo and G. A. Swan, *J. Chem. Soc.* 487 (1949).

¹⁹⁵ E. Schlittler and T. Allemann, *Helv. Chim. Acta* **31**, 128 (1948).

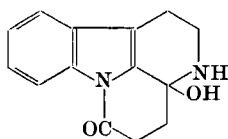
¹⁹⁶ P. L. Julian, W. J. Karpel, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.* **70**, 2834 (1948).

¹⁹⁷ O. E. Edwards and L. Marion, *J. Am. Chem. Soc.* **71**, 1694 (1949).

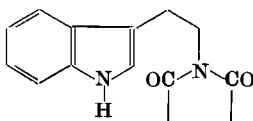
¹⁹⁸ J. Jost, *Helv. Chim. Acta* **32**, 1297 (1949).

homophthalimide **101** can also be cyclized directly.¹⁹⁹ An intermediate in the reaction, the dihydro- β -carbolinium derivative **103** ($R = OCH_3$), which on treatment with base was cyclized to **106** ($R = OCH_3$), has been isolated.⁷⁴ Evidence that ring closure does not lead to the alternative structure **105**, obtained from the isomeric homophthalamic acid **104**,¹⁹⁷ has been presented.¹⁹⁴

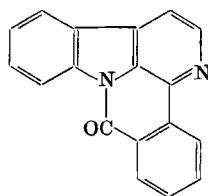
Related to this dihydro- β -carboline synthesis is a report²⁰⁰ that condensation of succinic anhydride and of phthalic anhydride with tryptamine leads directly to β -carboline derivatives. Products with molecular formulas $C_{14}H_{14}O_2N_2$, melting at 172° , and $C_{18}H_{10}ON_2$, melting at 227 – 228° , respectively, were isolated when tryptamine was heated at 200° for 9 hours with succinic anhydride and with phthalic anhydride. Structures **107** and **109** were tentatively assigned to the two products, but no structural proof was offered. The substance corresponding to the formula $C_{14}H_{14}O_2N_2$ was in fact β -(3-indolyl) ethylsuccinimide (**108**).^{200a} The structure of the product with the formula $C_{18}H_{10}ON_2$ remains to be confirmed.



[107]

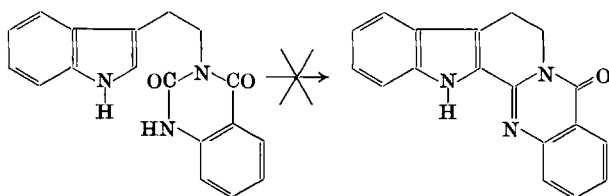


[108]



[109]

An early attempt to synthesize rutaecarpine (**111**) from the urea derivative **110** by a method analogous to that of Clemo and Swan was unsuccessful.²⁰¹



[110]

[111]

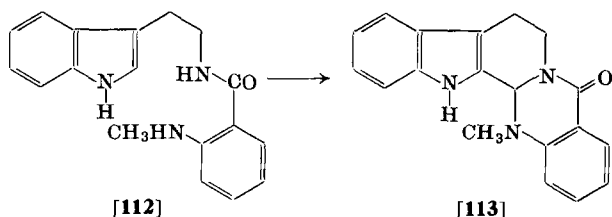
¹⁹⁹ E. Schlittler and R. Speitel, *Helv. Chim. Acta.* **31**, 1199 (1948).

²⁰⁰ L. Marion and R. H. F. Manske, *Can. J. Research* **16B**, 432 (1938).

^{200a} L. Marion and I. D. Spenser, unpublished results (1953).

²⁰¹ Y. Asahina and S. Ishimasa, *J. Pharm. Soc. Japan* **46**, 625 (1926).

Evodiamine (**113**) was synthesized by a Bischler-Napieralski type reaction from the amide **112** and ethyl orthoformate.²⁰²



A second direct route to an extended 3,4-dihydro- β -carbolinium system (**120**) using the Bischler-Napieralski ring closure is based on the cyclization of intermediates of general structure **118**. Three approaches to intermediates of this type have been developed in connection with stereospecific syntheses in the indole alkaloid field. The first approach, introduced independently by Stork and Hill^{154, 155} and by van Tamelen and co-workers^{165, 166, 203} and often used since,^{164, 204, 205} consists of the alkylation of tryptamine with a δ -bromo ester (e.g. **116**) followed by spontaneous lactamization of the product (**115**).

The second approach, developed by Woodward and co-workers³⁴ and repeatedly applied by others,^{35, 158-161} involves the condensation of tryptamine with an aldehyde derivative (e.g. **117**) followed by sodium borohydride reduction of the resulting Schiff's base **114** and lactamization of the reduction product **115**.

The most recent method is a Mannich reaction of tryptamine, formaldehyde, and the β -keto ester **119**, which yields the desired lactam **118** in one step.⁵⁷

Application of the Bischler-Napieralski reaction to amides of tryptophan has been investigated. The cyclodehydration of acetyltryptophan under conventional conditions proved unsuccessful.^{39, 40} Attempted ring closure of acetyltryptophan²⁰⁶ or its ethyl ester²⁰⁷ was accompanied by decarboxylation and aromatization, yielding

²⁰² Y. Asahina and T. Ohta, *Ber.* **61**, 319 (1928).

²⁰³ E. E. van Tamelen, M. Shamma, and P. Aldrich, *J. Am. Chem. Soc.* **78**, 4628 (1956).

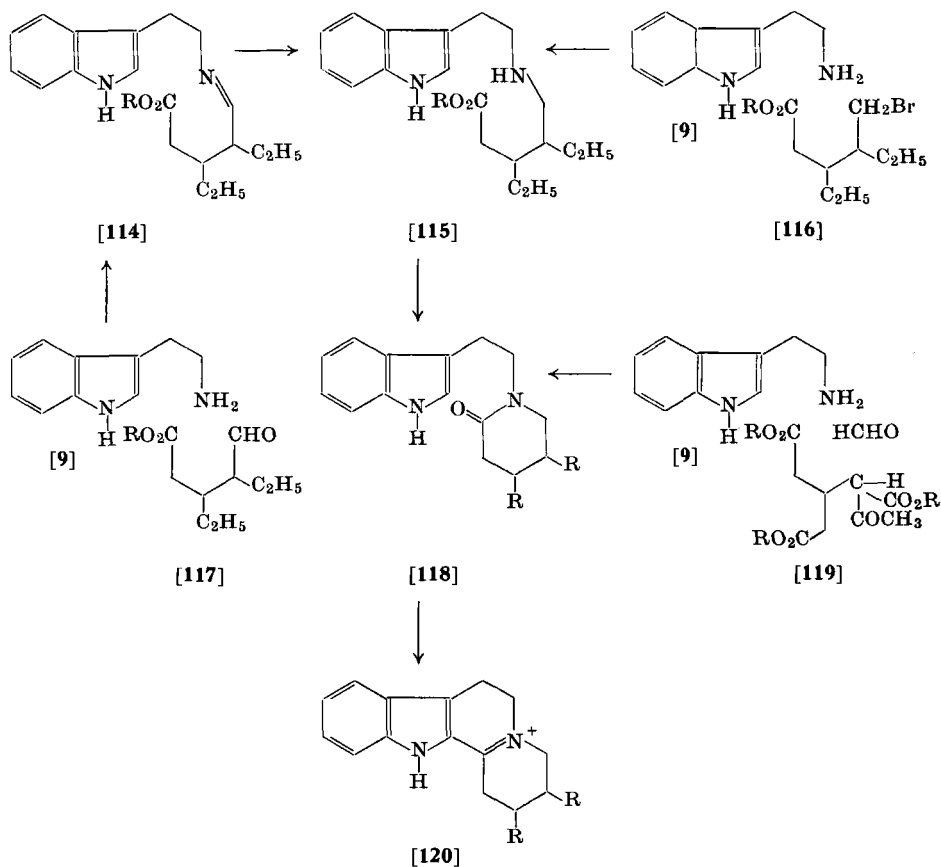
²⁰⁴ A. Le Hir, M.-M. Janot, and D. Van Stolk, *Bull. Soc. Chim. France* 551 (1958).

²⁰⁵ S. de Groot and J. Strating, *Rec. Trav. Chim.* **80**, 121 (1961).

²⁰⁶ H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.* **72**, 2962 (1950).

²⁰⁷ I. Murakoshi, *Yakugaku Zasshi* **77**, 550 (1957); *Chem. Abstr.* **51**, 14720 (1957).

1-methyl- β -carboline instead of the desired 1-methyl-3,4-dihydro- β -carboline-3-carboxylic acid (cf. Section III, E, 1, e). The latter product was finally obtained from acetyltryptophan by treatment at moderate temperature with a mixture of phosphorus oxybromide and polyphosphoric acid⁸⁵ or with trifluoroacetic acid.²⁰⁸ Much earlier the same

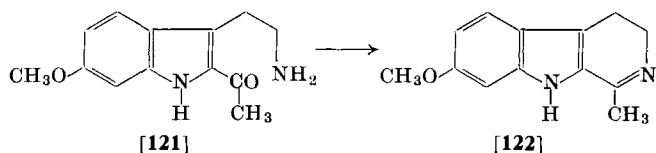


product had been obtained,²⁰⁹ but its structure had not been recognized. *N* β -Formyl- and *N* β -propionyl-tryptophan have been cyclized to the corresponding 3,4-dihydro- β -carbolinecarboxylic acids.⁴²

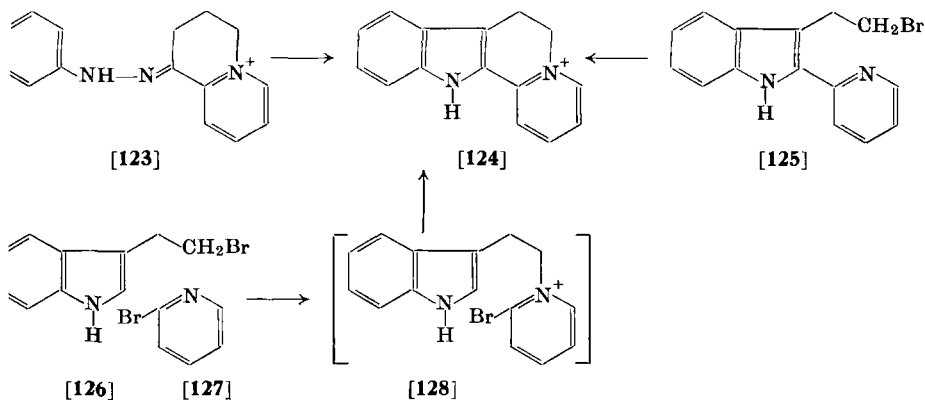
²⁰⁸ R. A. Uphaus, L. I. Grossweiner, J. J. Katz, and K. D. Kopple, *Science* **129**, 641 (1959).

²⁰⁹ F. Wrede and F. Feuerriegel, *Ber.* **66**, 1073 (1933).

b. *Other Syntheses.* The final step of the original synthesis of harmaline (**122**) consisted of the spontaneous intramolecular cyclization of 2-acetyl-3- β -aminoethyl-6-methoxyindole (**121**), obtained in an eight-step sequence of conventional reactions.²¹⁰



A number of instances in which application of the Fischer synthesis led to extended 3,4-dihydro- β -carbolinium derivatives have been recorded. Typical for this approach is the ring closure of the phenylhydrazones **123** to the expected tetracyclic product **124**.²¹¹⁻²¹⁴



Two other approaches to the same type of end-product have been recorded. In the first a 2-(2-pyridyl)- or 2-(1-isoquinolyl)-indole is converted, by way of the corresponding gramine, in conventional steps into the 3-(β -bromoethyl) derivative (e.g. **125**), which cyclizes to the 3,4-dihydro- β -carbolinium salt **124**.^{167, 168} The other is based on a condensation of 3-(β -bromoethyl)indole (**126**) with a 2-halopyridine,

²¹⁰ R. H. F. Manske, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* 1 (1927).

²¹¹ E. E. Glover and G. Jones, *J. Chem. Soc.* 1750 (1958).

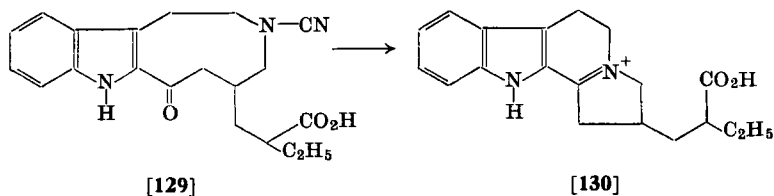
²¹² K. B. Prasad and G. A. Swan, *J. Chem. Soc.* 2024 (1958).

²¹³ G. A. Swan, *J. Chem. Soc.* 2038 (1958).

²¹⁴ R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.* **23**, 435 (1958).

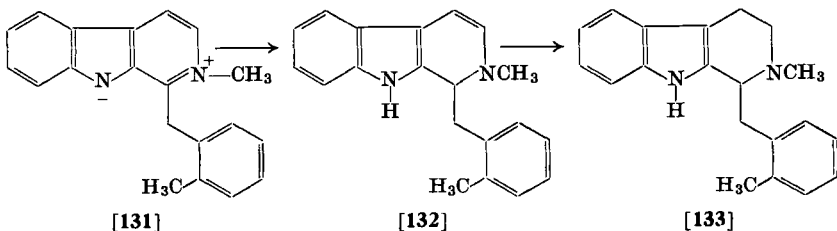
2-haloquinoline, or 1-haloisoquinoline (e.g. **127**) to yield the 3,4-dihydro- β -carbolinium salt **124**, presumably by way of the intermediate **128**.^{169, 170, 215, 215a}

In the course of a study into the structure of ibogamine and related compounds Bartlett *et al.*²¹⁶ found that if the keto acid **129** was heated with 2*N* hydrochloric acid in a sealed tube at 100° for 12 hours the tetracyclic 3,4-dihydro- β -carboline derivative **130** was formed.



2. From Other Oxidation States of the Preformed Ring System

a. *From Carbolines.* No method for the partial reduction of a fully aromatic β -carboline to a dihydro derivative has been described. The only instance where such a reduction may have occurred is in the reaction with sodium dithionite of the anhydro-base (**131**) derived from 1-*o*-methylbenzyl- β -carboline methiodide, which yielded a yellow, strongly reducing, fluorescent product, which on hydrogenation gave 2-methyl-1-*o*-methylbenzyl-1,2,3,4-tetrahydro- β -carboline (**133**). The nature of this substance, to which structure **132** was assigned¹³⁸ as one possibility, requires confirmation.



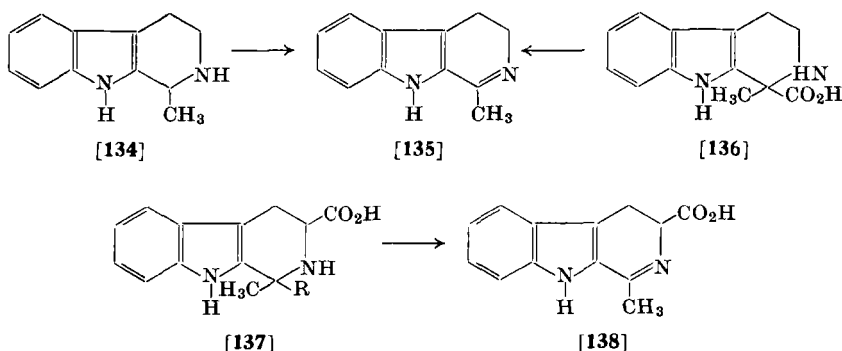
b. *From Tetrahydrocarbolines.* 1,2,3,4-Tetrahydro- β -carbolines have been converted into the corresponding 3,4-dihydro derivatives in a

²¹⁵ Y. Ban and M. Seo, *Tetrahedron* **16**, 11 (1961).

^{215a} Y. Ban and M. Seo, *J. Org. Chem.* **27**, 3380 (1962).

²¹⁶ M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.* **80**, 126 (1958).

number of instances. Only a few examples of this oxidation have been reported with simple tetrahydro- β -carbolines. Thus, 7-methoxy-1-methyl-1,2,3,4-tetrahydro- β -carboline yields harmaline¹⁵⁰ and 1-methyl-1,2,3,4-tetrahydro- β -carboline (**134**) yields 1-methyl-3,4-dihydro- β -carboline (**135**)²⁶ on treatment with permanganate in cold acetone. The latter compound is also obtained by oxidative decarboxylation of 1-methyl-1,2,3,4-tetrahydro- β -carboline-1-carboxylic acid (**136**).²⁶ Palladium dehydrogenation of 1-methyl-1,2,3,4-tetrahydro- β -carboline-3-carboxylic acid (**137**; R = H) or of 1-methyl-1,2,3,4-tetrahydro- β -carboline-1,3-dicarboxylic acid (**137**; R = COOH) gave 1-methyl-3,4-dihydro- β -carboline-3-carboxylic acid (**138**).⁴²

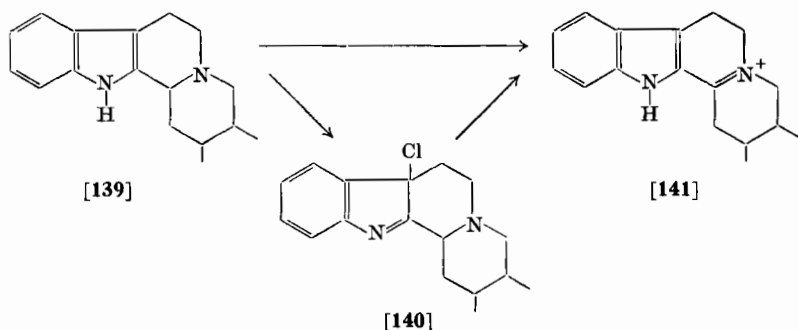


Similar oxidative reactions have been studied more thoroughly in the pentacyclic series of tetrahydro- β -carbolines, and general methods are available.

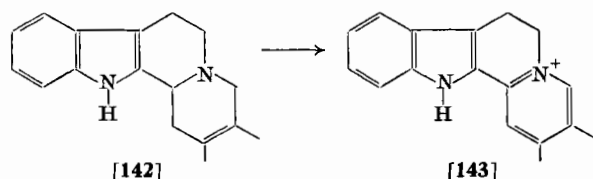
Those epimers of 1,2,3,4-tetrahydro- β -carbolines of general structure **139**, in which the hydrogen on carbon-1 of the carboline moiety is axial, are converted into the corresponding 3,4-dihydro- β -carbolinium salts (**141**) by mercuric acetate oxidation.^{115, 121, 156, 162} Sodium dichromate in aqueous acetic acid has been reported to be a superior reagent for this oxidation.²¹⁷ *t*-Butyl hypochlorite reacts with either of the two carbon-1 epimers to give a chloroindolenine (**140**), which on treatment with acid yields the dihydro- β -carbolinium salt (e.g. **141**).^{157, 218}

²¹⁷ M. M. Robison, R. A. Lucas, H. B. MacPhillamy, R. L. Dziemian, I. Hsu, and R. J. Kiesel, *J. Am. Chem. Soc.* **83**, 2694 (1961).

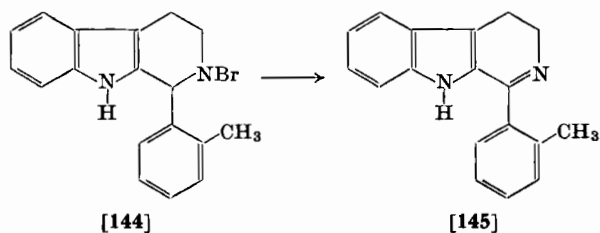
²¹⁸ N. Finch and W. I. Taylor, *J. Am. Chem. Soc.* **84**, 3871 (1962).



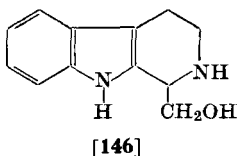
Catalytic dehydrogenation using palladium/maleic acid has been used to convert tetrahydro- β -carbolines of general structure **142** into the dihydro- β -carbolinium salts (**143**)^{115, 103} A similar transformation has been carried out by oxidation with iodine.^{108, 109, 214}



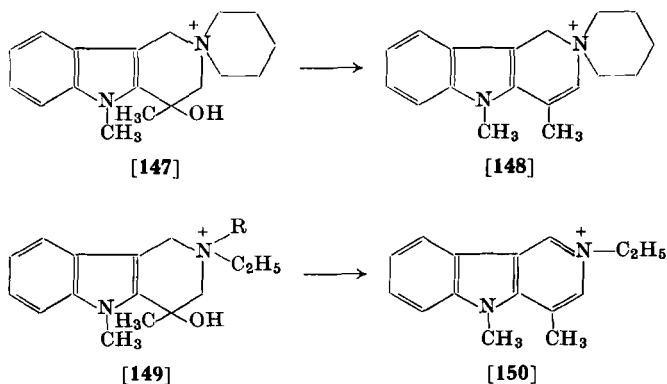
The photochemical conversion of the 2-bromo derivative **144**, derived from 1-*o*-methylphenyl-1,2,3,4-tetrahydro- β -carboline by treatment with hypobromite, into a dihydro- β -carboline, regarded as **145**, has been reported.³¹



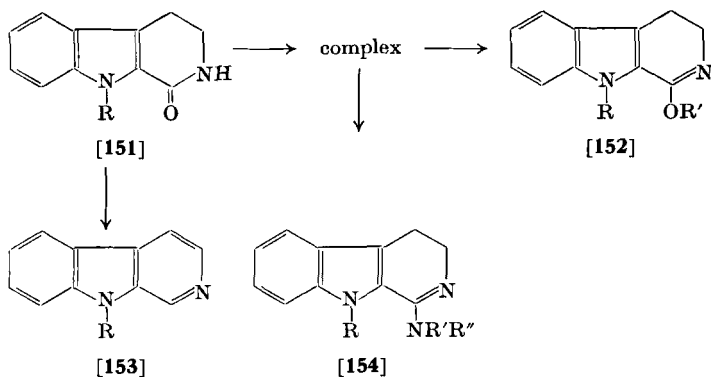
Non-oxidative conversion of a tetrahydro- β -carboline into a 3,4-dihydro derivative has also been described. Dehydration of 1-hydroxymethyl-1,2,3,4-tetrahydro- β -carboline (**146**) yielded 1-methyl-3,4-dihydro- β -carboline (**135**). Harmaline and 1-methyl-3,4-dihydro- β -carboline-3-carboxylic acid were obtained in an analogous manner.²⁶



Dehydration of a spirocyclic quaternary salt such as **147** gives rise to a 3,4-dihydro- γ -carboline (**148**).⁸⁶ This reaction is not, however, of general applicability since both **149** ($R = C_2H_5$) and **149** ($R = CH_2C_6H_5$) yield the fully aromatic carbolinium salt **150** under the same conditions.



c. *From Oxotetrahydro- β -carbolines.* When an *ind-N*-alkyl-1,2,3,4-tetrahydro-1-oxo- β -carboline (**151**) is heated at 50–80° with phosphorus oxychloride and then treated with ether or petroleum ether, a



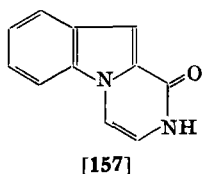
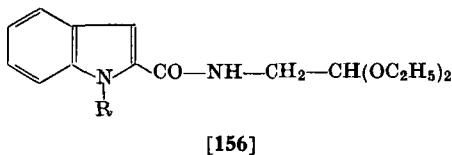
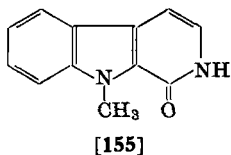
complex is obtained which reacts with an alcohol to give the corresponding *ind-N*-alkyl-1-alkoxy-3,4-dihydro- β -carboline (**152**) and with an amine to yield the 1-amino-3,4-dihydro compound (**154**).²¹⁹ If, on the other hand, **151** is boiled under reflux with phosphorus oxychloride the fully aromatic *ind-N*-alkyl- β -carboline (**153**) is formed.^{175, 220}

D. OXO-DIHYDRO AND -TETRAHYDRO DERIVATIVES

Most of the early work carried out on the synthesis of these compounds was aimed at the elucidation of the structures of various harmala and other alkaloids. It will not be presented here in historical sequence but rather in a systematic fashion according to the starting materials and the synthetic methods used.

1. From Non-Carboline Precursors

a. *1-Oxo-1,2-dihydro- β -carbolines*. The various attempts to synthesize 1-oxo-1,2-dihydro- β -carbolines *via* a Pomeranz-Fritsch type synthesis are of special interest in that they bring to light some rather



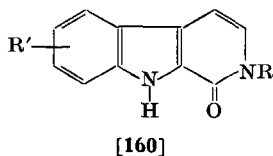
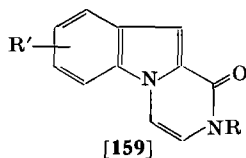
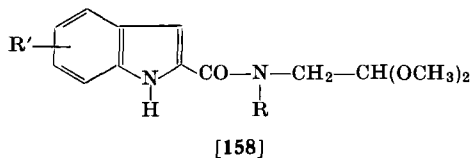
important aspects of the chemistry of indoles. This approach was first investigated by Kermack *et al.*²²¹ who found that if the acetal **156** (R = H) was treated with alcoholic hydrogen chloride at 40–45° the

²¹⁹ H. Henecka, R. Lorenz, and H. Timmler, German Patent 1,045,511 (1958) [*Chem. Abstr.* **55**, 5543 (1961)]; R. Lorenz, H. Timmler, and H. Henecka, German Patent 1,039,065 (1958) [*Chem. Abstr.* **54**, 22687 (1960)].

²²⁰ H. Timmler, R. Lorenz, and H. Henecka, German Patent 1,044,821 (1958); *Chem. Abstr.* **55**, 3642 (1961).

²²¹ W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **119**, 1602 (1921).

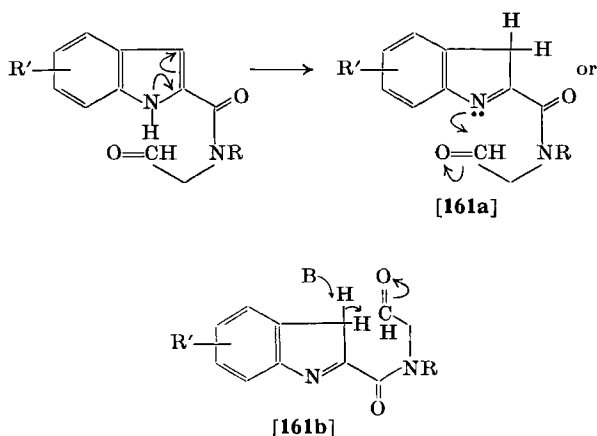
indolo[1,2-*a*]pyrazinone **157**, resulting from cyclization at the indolic NH, was obtained as the sole product. On the other hand, if the *N*-methylindole derivative **156** ($R = CH_3$) was used, the product formed was 9-methyl-1-oxo-1,2-dihydro- β -carboline (**155**). This work was extended by the same authors¹²⁹ to a number of substituted derivatives (**158**) of **156** to establish what factors would favor the preferential formation of either the indolopyrazinone **159** or the β -carboline derivatives **160**. One of their most striking results was the observation that when the amide nitrogen was unsubstituted (**158**; $R = R' = H$) the sole product formed was **159** ($R = R' = H$), whereas if the amide nitrogen atom bore a methyl group (**158**; $R = CH_3$, $R' = H$) the only product formed was **160** ($R = CH_3$, $R' = H$). A



6-methoxy substituent in the indole ring (**158**; $R = CH_3$, $R' = 6-OCH_3$) counterbalanced to a certain extent the effect of the amide *N*-methyl group, since, in its presence, a mixture of the corresponding indolopyrazinone and β -carboline was formed. The effect of methoxyl substituents in the indole ring was investigated further.²²² A 4-methoxyl group in **158** ($R = CH_3$, $R' = 4-OCH_3$) led to the formation of, at most, traces of the indolopyrazinone, the only product actually isolated being 5-methoxy-1-oxo-1,2-dihydro- β -carboline. A 5-methoxyl group directed cyclization equally at positions 1 and 3, while a 7-methoxyl group in **158** led to the formation of **159** and **160** ($R = CH_3$, $R' = 8-OCH_3$) in the ratio of 1 : 4. In the absence of the amide *N*-methyl group, cyclization took place exclusively at the indole nitrogen atom even when a 5-methoxyl group was present. Reinvestigation of the cyclization of **156** ($R = H$) in the presence of either alcoholic hydrogen

²²² K. G. Blaikie and W. H. Perkin, Jr., *J. Chem. Soc.* **125**, 296 (1924).

chloride or ethereal sulfuric acid showed²²³ that both **154** and 1-oxo-1,2-dihydro- β -carboline were formed, in the ratio of 4:1. The latter was detected spectroscopically and isolated. An attempt to cyclize 6-cyanoindolo-2-carboxydimethylacetalylamide (**158**; R = H, R' = 6-CN) failed and it was concluded²²⁴ that the 6-cyano group inhibits ring formation by decreasing the reactivity of the hydrogen atoms at carbons 1 and 3. When there is a 5-cyano group in an *N*-benzylacetalylamide ring closure does proceed with the formation of only one isomer,



the oxodihydro- β -carboline.²²⁵ An unsubstituted 5-position or a 5-carbethoxyamino group (**158**; R = CH₂C₆H₅, R' = NH—CO₂C₂H₅) apparently led to the formation of a mixture of products on ring closure, but in each reaction only the oxodihydro- β -carboline was isolated and identified by its ultraviolet absorption spectrum.

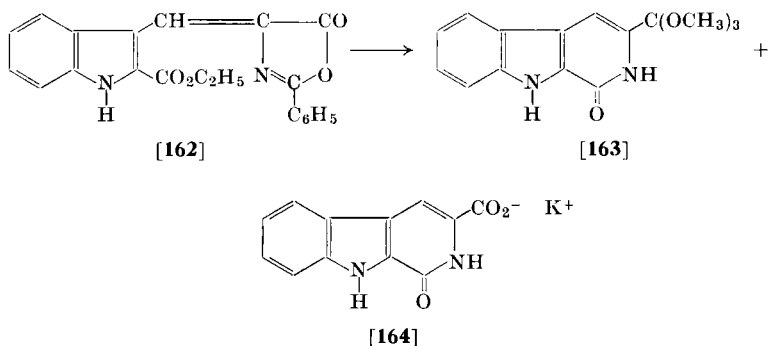
The influence of substituents in the benzene ring upon the ease and direction of ring closure might, to a certain extent, be explained if the reactions involve the formation of an intermediate of the type **161a** or **161b**. Electron-attracting or -donating substituents might then exert an effect on either the protonation at carbon-3 or the electron-donating ability of the nitrogen atom, or on both. The interesting effect of an amide *N*-alkyl group upon the direction of ring closure is difficult to explain and deserves further investigation.

²²³ J. R. Johnson, A. A. Larsen, A. D. Holley, and K. Gerzon, *J. Am. Chem. Soc.* **69**, 2364 (1947).

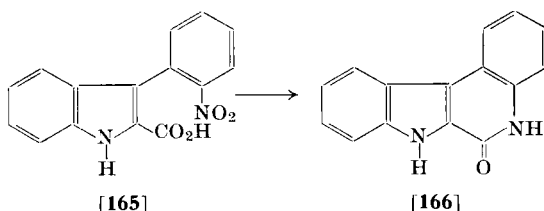
²²⁴ W. O. Kermack, *J. Chem. Soc.* **125**, 2285 (1924).

²²⁵ H. G. Lindwall and G. J. Mantell, *J. Org. Chem.* **18**, 345 (1953).

Another approach to the 1-oxo-1,2-dihydro- β -carboline system is that due to King and Stiller.²²⁶ When 2-ethoxycarbonyl-3-formylindole is condensed with hippuric acid the azlactone **162** is formed, which, with 10% methanolic potassium hydroxide, gives a mixture of the orthoester **163** and the potassium salt **164**.



Polycyclic derivatives have been prepared by straightforward amide formation.^{25, 227, 228} The tetracyclic amide **166** was obtained by reductive cyclization of 3-*o*-nitrophenylindole-2-carboxylic acid (**165**).²²⁷ When 1-(2'-ethoxycarbonylskatyl)isoquinoline (**167**) was heated the pentacyclic β -carboline derivative **168** was formed.^{25, 229} If, however, **167** was first reduced with hydrogen in the presence of a platinum catalyst and the resulting tetrahydroisoquinoline (**169**) heated in boiling tetralin, cyclization and partial dehydrogenation to a compound assigned structure **170** on the basis of its ultraviolet absorption spectrum was observed.²²⁸

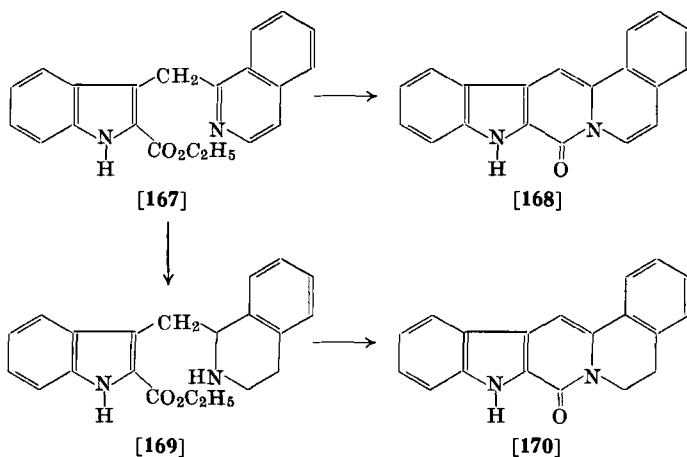


²²⁶ H. King and E. T. Stiller, *J. Chem. Soc.* 466 (1937).

²²⁷ W. O. Kernack and R. H. Slater, *J. Chem. Soc.* 32 (1928).

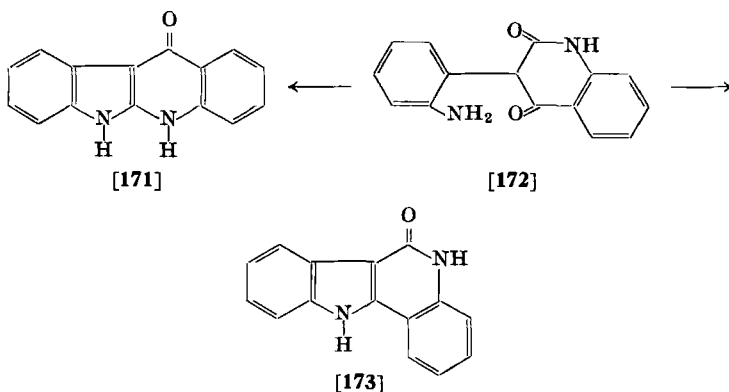
²²⁸ V. Boekelheide and C. Ainsworth, *J. Am. Chem. Soc.* **72**, 2134 (1950).

²²⁹ G. R. Clemo and J. C. Seaton, *J. Chem. Soc.* 2582 (1954).



Pyrolytic ring closure of 3-*o*-aminophenyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**172**) gave a mixture of the α - and γ -oxodihydro-carbolines **171** and **173**.²³⁰

b. *1-Oxo-1,2,3,4-tetrahydro-β-carbolines*. These compounds were first prepared from ethyl β -3-indolylpropionates *via* the azide and a Curtius rearrangement.^{231, 232, 233} A somewhat improved method²³⁴



²³⁰ H. de Diesbach, J. Gross, and W. Tschannen, *Helv. Chim. Acta* **34**, 1050 (1951).

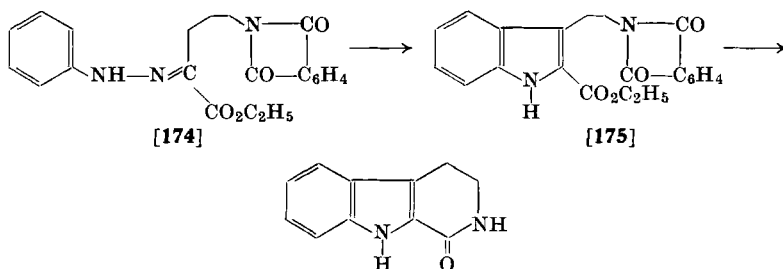
²³¹ R. H. F. Manske and R. Robinson, *J. Chem. Soc.* 240 (1927).

²³² H. S. Barrett, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* 2942 (1929).

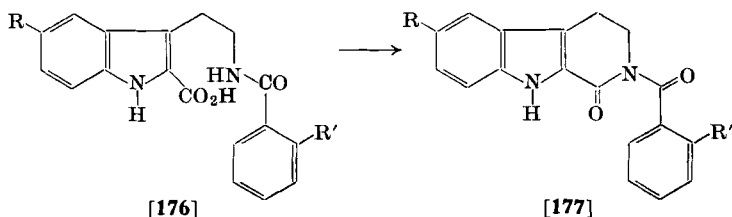
²³³ R. H. F. Manske, *Can. J. Research* **4**, 591 (1931).

²³⁴ S. Keimatsu, S. Sugawara, and G. Kasuya, *J. Pharm. Soc. Japan* **48**, 762 (1928); *Chem. Abstr.* **23**, 834 (1929).

employed a Japp-Klingemann reaction to obtain the α -keto- δ -amino-valerate phenylhydrazone derivative **174** which then underwent a Fischer cyclization to give the tryptamine derivative **175**; the latter, on treatment with ethanolic hydrazine followed by mineral acid, gave the required 1-oxo-1,2,3,4-tetrahydro- β -carboline. A similar method was used¹⁷⁹ to prepare a 1-oxo-1,2,3,4,4a,9a-hexahydro-9,9a-dehydro- β -carboline derivative.



Straightforward lactam formation has been used in a few instances. Thus **176** ($R = H$, $R' = NO_2$)^{235, 236} with phosphorus oxychloride and **176** [$R = OCH_3$, $R' = N(CH_3)_2$]¹⁷⁵ on treatment with polyphosphoric acid give the corresponding 2-aryl-1-oxo-1,2,3,4-tetrahydro- β -carboline (**177**). In the latter instance the use of acetic anhydride

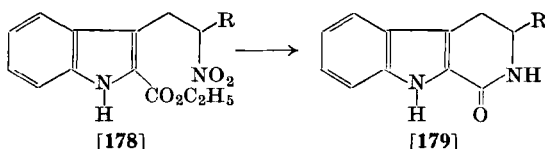


instead of polyphosphoric acid leads to the formation of the *ind-N*-acetyl derivative. In an interesting study of the selective reduction of the 3- β -nitroethylindolecarboxylic ester **178**, it was found that reduction with zinc and acetic acid gave 41–59% yields of the corresponding 1-oxo-1,2,3,4-tetrahydro- β -carboline (**179**).²³⁷

²³⁵ Y. Asahina and T. Ohta, *J. Pharm. Soc. Japan* **48**, 313 (1928); *Chem. Abstr.* **22**, 3393 (1928).

²³⁶ Y. Asahina, T. Irie, and T. Ohta, *J. Pharm. Soc. Japan* **47**, 359 (1927); *Chem. Abstr.* **21**, 3054 (1927).

²³⁷ D. V. Young and H. R. Snyder, *J. Am. Chem. Soc.* **83**, 3160 (1961).



The most general and widely used approach to the 1-oxo-1,2,3,4-tetrahydro- β -carbolines at present available is that developed by Abramovitch.^{172, 173, 238} 2,3-Dioxopiperidine 3-phenylhydrazones (**181**) is prepared by a Japp-Klingemann reaction from 2-oxopiperidine-3-carboxylic acid (**180**) and benzenediazonium chloride. Fischer cyclization of the hydrazone gives the required 1,2,3,4-tetrahydro-1-oxo- β -carboline (**183**). The oxotetrahydro- β -carboline **183** and its derivatives are very convenient starting materials for the synthesis of tryptamines as well as of rutaecarpine and related compounds, and this method has been used extensively since it permits of a wide variation both in the diazonium salt and in the piperidone used.^{175, 239-244} This synthetic route is exploited in numerous patents.²⁴⁵ The only reported failures to effect cyclization were in the cases when 2,3-dioxo-4-methylpiperidine 3-phenylhydrazone and 2,3-dioxopiperidine 3-(*o*-acetylphenyl)hydrazone were used; the former rearranged to a more stable form of the phenylhydrazone,²⁴⁶

²³⁸ R. A. Abramovitch and J. M. Muchowski, *Can. J. Chem.* **38**, 554, 557 (1960).

²³⁹ Z. Pelchowicz and E. D. Bergmann, *J. Chem. Soc.* 847 (1959).

²⁴⁰ E. Adlerová, I. Ernest, V. Hněvsová, J. O. Jilek, L. Novák, J. Pomykáček, M. Rajšner, J. Sova, S. J. Vojdělek, and M. Protiva, *Collection Czech. Chem. Commun.* **25**, 784 (1960).

²⁴¹ L. De Bellis and M. L. Stein, *Ann. Chim. (Rome)* **51**, 663 (1961); *Chem. Abstr.* **56**, 11544 (1962).

²⁴² A. G. Terzian, R. R. Safrazbekian, R. S. Sukasian, and G. T. Tatevosian, *Experientia* **17**, 493 (1961); *Izv. Akad. Nauk. Arm. SSR, Khim. Nauki* **14**, 261 (1961); *Chem. Abstr.* **57**, 8531 (1962).

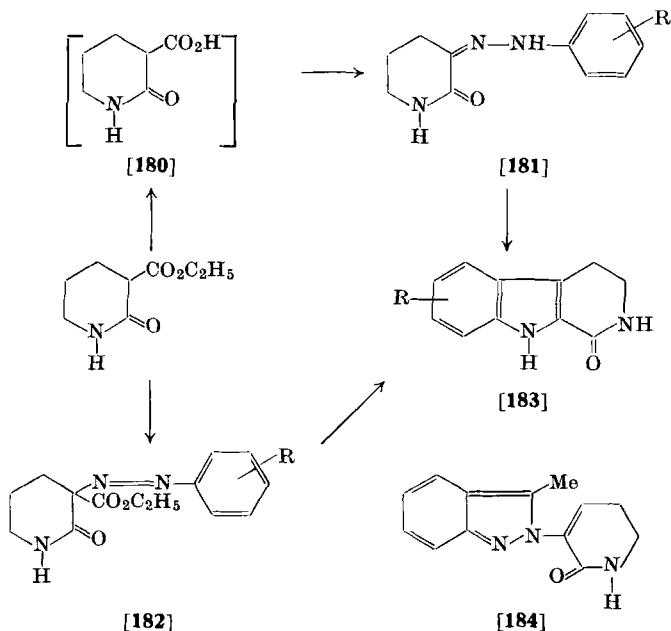
²⁴³ S. J. Fusco, *Dissertation Abstr.* **22**, 3397 (1962).

²⁴⁴ J. Shavel, Jr., M. von Strandtmann, and M. P. Cohen, *J. Am. Chem. Soc.* **84**, 881 (1962); M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Med. Chem.* **6**, 719 (1963).

²⁴⁵ G. Nominé and L. Pénasse, French Patent 1,181,214 (1959), French Patent 1,184,706 (1959) [*Chem. Abstr.* **55**, 14480 (1961)]; French Patent 1,188,326 (1959) [*Chem. Abstr.* **54**, 24800 (1960)]; A. Allais, French Patent 1,180,512 (1959) [*Chem. Abstr.* **55**, 14480 (1961)]; I. J. Pachter and R. F. Raffauf, U.S. Patent 2,858,251 (1958) [*Chem. Abstr.* **53**, 6271 (1959)]; M. Protiva, I. Ernest, V. Hněvsová, L. Novák, and M. Rajšner, Czechoslovakian Patent 96,101 (1960) [*Chem. Abstr.* **55**, 10478 (1961)].

²⁴⁶ R. A. Abramovitch, *Can. J. Chem.* **36**, 354 (1958).

whereas the latter is reported to give 3-methyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2*H*-indazole (**184**).²⁴⁴ In a modification of the procedure introduced by Henecka *et al.*,²⁴⁷ the Japp-Klingemann reaction was carried out on the 2-oxopiperidine-3-carboxylic ester directly before saponification to give the 2-oxo-3-phenylazopiperidine-3-carboxylic ester **182**, which was cyclized as before to the 1,2,3,4-tetrahydro-1-oxo- β -carboline (**183**).

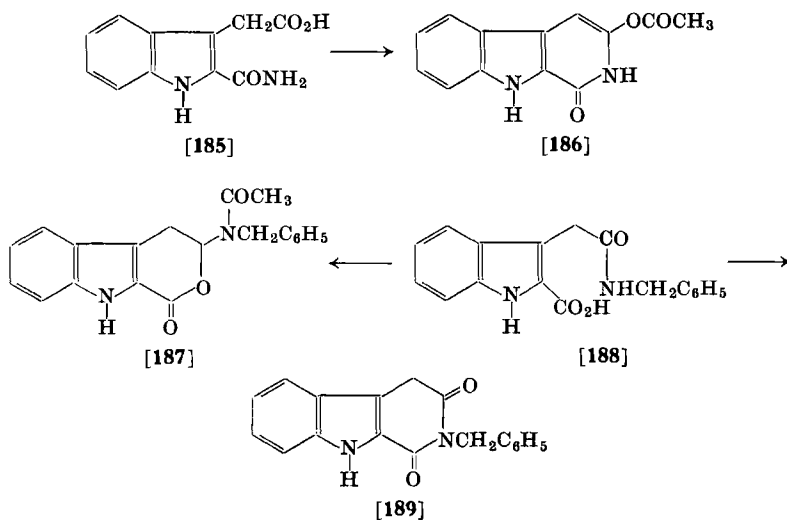


c. *1,3-Dioxo-1,2,3,4-tetrahydro- β -carboline*. An attempt to prepare a dioxo- β -carboline was first made by Kermack *et al.*²²¹ When 2-carboxyindole-3-acetic acid was treated with acetic anhydride and the product fused with ammonium acetate, an amide tentatively formulated as **185**, was obtained. This, on treatment with acetic anhydride and acetyl chloride, gave a compound to which the structure **186** was assigned, i.e., an enol acetate of the expected 1,3-dioxo-1,2,3,4-tetrahydro- β -carboline.

2-Benzyl-1,3-dioxo-1,2,3,4-tetrahydro- β -carboline (**189**) was prepared by heating the benzylamide **188** with polyphosphoric acid on a

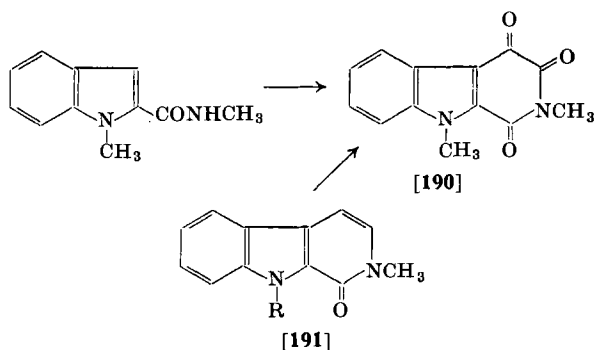
²⁴⁷ H. Henecka, H. Timmler, R. Lorenz, and W. Geiger, *Chem. Ber.* **90**, 1060 (1957).

water-bath for 1.5 hours. Treatment of **188** with acetic anhydride and acetyl chloride gave the lactone **187** instead.¹⁵²



An attempt to prepare a 1,4-dioxo-1,2,3,4-tetrahydro- β -carboline was unsuccessful.²⁴⁸

d. *1,3,4-Trioxo-1,2,3,4-tetrahydro- β -carbolines*. When 1-methylindole-2-carboxylic acid methylamide was treated with ethoxalyl chloride, 2,9-dimethyl-1,3,4-trioxo-1,2,3,4-tetrahydro- β -carboline (**190**) was obtained.²⁴⁸ Structure **190** was confirmed by the synthesis of



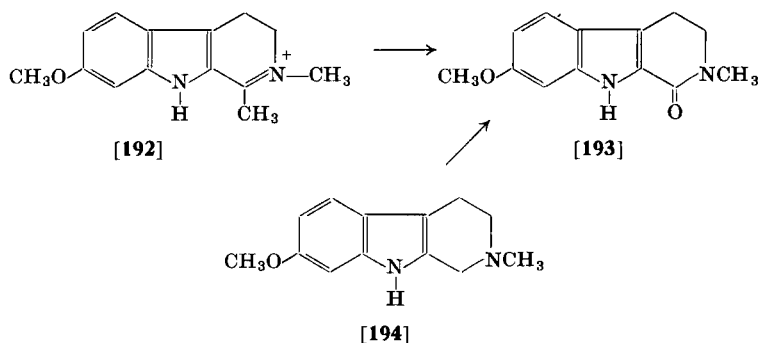
²⁴⁸ J. R. Johnson, R. B. Hasbrouck, J. D. Dutcher, and W. F. Bruce, *J. Am. Chem. Soc.* **67**, 423 (1945).

the same product starting from a preformed β -carboline ring system: oxidation of 2,9-dimethyl-1-oxo-1,2-dihydro- β -carboline (**191**; R = CH₃) with chromic acid in acetic acid gave the required trioxo compound.

2. From Other Oxidation States of the Preformed Ring System

a. *1-Oxo-1,2-dihydro- β -carbolines*. Oxidation of 2-methyl- β -carbolinium methosulfate with alkaline ferricyanide gave 2-methyl-1-oxo-1,2-dihydro- β -carboline (**191**; R = H).¹²⁹ 1-Oxo-1,2-dihydro- β -carboline itself was obtained by heating 1-oxo-1,2,3,4-tetrahydro- β -carboline with palladium black at 190–195°.²⁴⁹

b. *1-Oxo-1,2,3,4-tetrahydro- β -carbolines*. When harmaline methosulfate (7-methoxy-1,2-dimethyl-3,4-dihydro- β -carbolinium methylsulfate; **192**) was oxidized with potassium permanganate in acetone 7-methoxy-2-methyl-1-oxo-1,2,3,4-tetrahydro- β -carboline (**193**) was obtained¹⁵⁰; the compound (**193**) was identical with the product



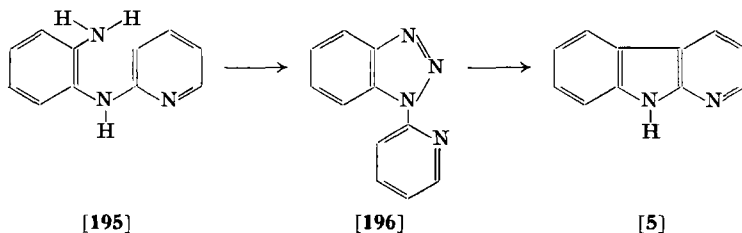
obtained by a similar oxidation of 7-methoxy-2-methyl-1,2,3,4-tetrahydro- β -carboline (**194**).¹²⁹ Similarly, oxidation of methylharmaline (7-methoxy-2-methyl-1-methylene-1,2,3,4-tetrahydro- β -carboline) gave **193**, whereas oxidation of 2-acetyl-7-methoxy-1-methylene-1,2,3,4-tetrahydro- β -carboline gave the *pyr-N*-acetyl compound in low yield.¹⁵¹ Related results were obtained by Gupta and Spenser¹⁹² who, in addition, found that distillation or alkaline ferricyanide oxidation of 2,9-dimethyl-1-hydroxy-1,2,3,4-tetrahydro- β -carboline gave the corresponding 1-oxo compound.

²⁴⁹ A. Chatterjee, S. Bose, and C. Ghosh, *Tetrahedron* **7**, 257 (1959).

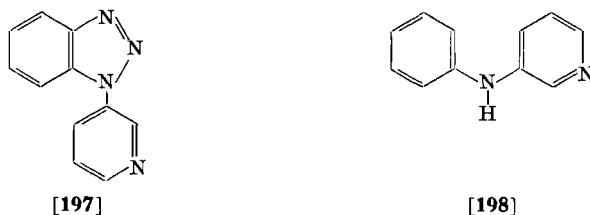
E. FULLY AROMATIC CARBOLINES

1. From Non-Carboline Precursors

a. *Graebe-Ullmann Type Reaction*. Application of the Graebe-Ullmann carbazole synthesis to the carboline series has led to syntheses of α -, β -, and γ -carboline. The synthesis of α -carboline from 1- α -pyridylbenztriazole (**196**) was first studied by Lawson *et al.*¹³⁵ *N*-2-Pyridyl-*o*-phenylenediamine (**195**) (prepared from 2-chloro- or



2-bromo-pyridine and *o*-phenylenediamine) is treated with nitrous acid and the resulting triazole is heated with fused zinc chloride to give the required α -carboline. The cyclization proceeds more smoothly if syrupy phosphoric acid^{136, 250-252} or polyphosphoric acid⁶ is used instead of zinc chloride. The preparation of β -carboline from 1- β -pyridylbenztriazole (**197**) was effected, albeit in very poor yield.²⁵³



When the triazole was heated with fused zinc chloride at 320° the main product was 3-anilinopyridine (**198**) together with a small amount of β -carboline. From the β -carboline mother liquors a small quantity of a product, m.p. 214—215°, was isolated. On the basis of the fact that this product was different from α - or γ -carboline, and though the

²⁵⁰ B. W. Ashton and H. Suschitzky, *J. Chem. Soc.* 4559 (1957).

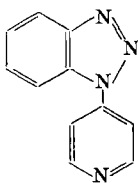
²⁵¹ S. J. Holt and V. Petrow, *J. Chem. Soc.* 922 (1948).

²⁵² R. R. Burtner, U.S. Patent 2,688,022 (1954); *Chem. Abstr.* **50**, 1925 (1956).

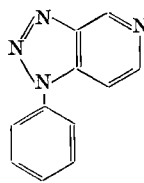
²⁵³ E. Späth and K. Eiter, *Ber.* **73**, 719 (1940).

micro-analytical results were rather poor, it was suggested that it was the then unknown δ -carboline. The same product, m.p. 212–213°, was also obtained when **197** was heated for 12 hours at 350°; no β -carboline was isolated under these conditions. On the other hand, the preparation of the product melting at 214–215° could not be repeated when the reaction was carried out on a larger scale.²⁵⁴ A similar cyclization of 4-methyl-1- β -pyridylbenztriazole gave 5-methyl- β -carboline as the main product together with a small amount of a compound which was regarded as 9-methyl- δ -carboline, although no analytical data were given.⁵ The assignment was based on the fact that the ultraviolet absorption curve of this product is very similar to that of 5-methyl- β -carboline. The ultraviolet absorption spectra of β - and δ -carbolines differ appreciably, however, so that it seems rather unlikely that this compound was 9-methyl- δ -carboline.

The extension of the method to the synthesis of γ -carboline from 1- γ -pyridylbenztriazole (**199**)¹⁰⁴ and of a 3,4-benz- γ -carboline from a 1-(4-quinolyl)benztriazole^{255, 256} proceeded smoothly. In an alternative approach excellent yields of γ -carboline were obtained by heating 1-phenylpyrido[3,4-*d*]v-triazole (**200**) at 320–350°.²⁵⁷ The synthesis of halogeno-substituted β - and γ -carbolines *via* the Graebe-Ullmann reaction has been reported.²⁵⁸



[199]



[200]

b. *Pschorr-Type Ring Closure*. This approach to the synthesis of the carboline ring system was first investigated by Abramovitch *et al.*²⁵⁹ When 2-amino-*N*-methyl-*N*-2'-pyridylaniline (**201**) was subjected to the conditions of the Pschorr cyclization the main product formed

²⁵⁴ K. Eiter, *Monatsh. Chem.* **79**, 17 (1948).

²⁵⁵ W. O. Kermack and J. F. Smith, *J. Chem. Soc.* 1999 (1930).

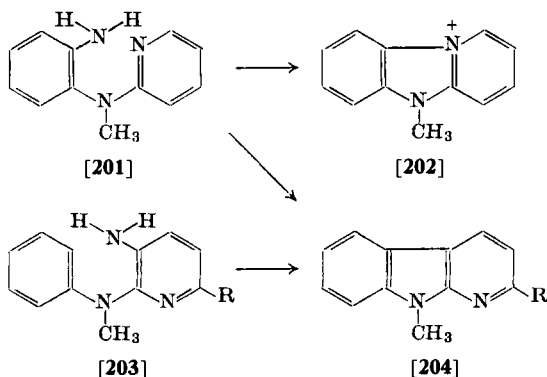
²⁵⁶ W. O. Kermack and N. E. Storey, *J. Chem. Soc.* 607 (1950).

²⁵⁷ O. Bremer, *Ann. Chem.* **514**, 279 (1934).

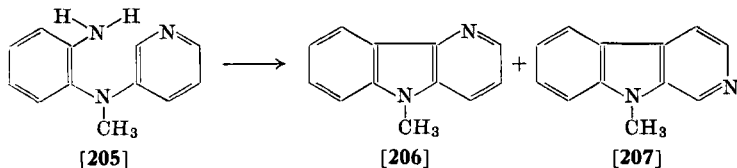
²⁵⁸ P. Nantka-Namirski, *Acta Polon. Pharm.* **18**, 391, 449 (1961); *Chem. Abstr.* **57**, 16553 (1962); **58**, 3424 (1963).

²⁵⁹ R. A. Abramovitch, D. H. Hey, and R. D. Mulley, *J. Chem. Soc.* 4263 (1954).

was 5-methylpyrido[1,2-*a*]benzimidazolium chloride (**202**) together with a much smaller (7%) amount of *ind-N*-methyl- α -carboline (**204**; R = H). The formation of **202** under the conditions used (action of heat on the diazonium chloride solution) is not unexpected since a heterolytic process is probably involved; the formation of the α -carboline derivative may well be due to a concurrent homolytic process (see, however, ref. 260a). To avoid the formation of **202**, *N*-(3-amino-2-pyridyl)-*N*-methylanilines (**203**) were used as the starting materials instead of **201**, and good yields of the corresponding α -carbolines were then obtained.



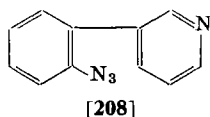
Decomposition of the diazonium salt of 2-amino-*N*-methyl-*N*-(3'-pyridyl)aniline (**205**) in aqueous acid solution with copper powder at room temperature gave overall yields of cyclized products consisting of a mixture of *ind-N*-methyl- δ -carboline (**206**) (47.5%) and *ind-N*-methyl- β -carboline (**207**) (25.5%), in agreement with the proposed homolytic character of the reaction under these conditions.²⁶⁰ This constituted the first unambiguous synthesis of a simple δ -carboline derivative.



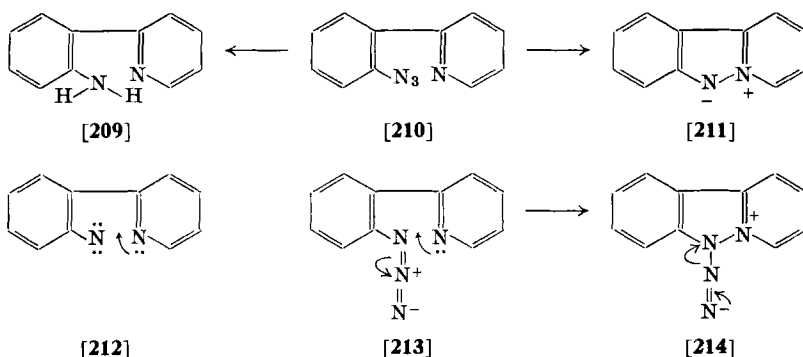
²⁶⁰ R. A. Abramovitch, *Can. J. Chem.* **38**, 557 (1960).

^{260a} R. A. Abramovitch and G. Tertzakian, *Tetrahedron Letters* 1511 (1963).

c. *Decomposition of Azides.* In an extension of a method for the synthesis of carbazole, thermal decomposition of 3-(2'-azidophenyl)pyridine (**208**) led to the formation of a mixture of α - (**5**) and γ -carboline (**7**).²⁶¹ On the other hand, it was reported that the thermal decomposition of 2-(2'-azidophenyl)pyridine (**210**) in decalin solution gave 2-*o*-aminophenylpyridine (**209**) instead of the expected δ -carboline, due to hydrogen abstraction from the solvent. Abramovitch and Adams²⁶² repeated this reaction but could not detect any primary



amine when the crude reaction product was chromatographed on a column of neutral alumina. The only product isolated (in 60% yield) was pyrido[1,2-*b*]indazole (**211**). This could have resulted either from the formation of an imido intermediate^{262a} (**212**) (in the singlet state and thus electrophilic) with evolution of nitrogen, followed by attack upon the pyridine nitrogen lone pair of electrons, or by a concerted attack by the pyridine nitrogen upon the azide group and elimination



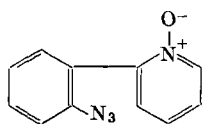
of a molecule of nitrogen (**213** \rightarrow **214**). When the pyridine ring nitrogen atom was blocked by the expedient of forming the *N*-oxide (**215**), thermal decomposition of the azide in decalin solution gave a crude mixture from which δ -carboline and δ -carboline *pyr-N*-oxide (**216**)

²⁶¹ P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.* **73**, 2626 (1951).

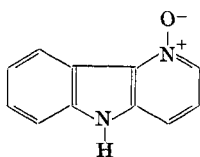
²⁶² R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.* **39**, 2516 (1961).

^{262a} R. A. Abramovitch and B. A. Davis, *Chem. Rev.* in press (1964).

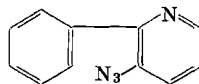
were isolated in low yield by chromatography on alumina.²⁶² A better preparation of δ -carboline was the thermal decomposition of 3-azido-2-phenylpyridine (**217**), but the yields were not reproducible, varying from good to very poor.²⁶³



[215]



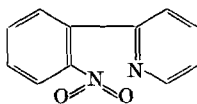
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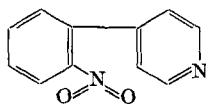
[217]

d. *The Action of Ferrous Oxalate on Nitro Compounds.* In an attempt to extend the Waterman and Vivian carbazole synthesis²⁶⁴ to the synthesis of δ -carboline, 2-*o*-nitrophenylpyridine (**218**) was heated with ferrous oxalate: the only product formed was pyrido[1,2-*b*]indazole (**211**),^{262, 265} presumably *via* the intermediate **212**.^{262a}

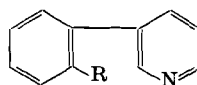
Similarly, cyclization of 2-*o*-nitrophenylpyridine *N*-oxide gave **211**, deoxygenation preceding cyclization, though in this case a trace of δ -carboline was isolated.²⁶² The cyclization of 4-*o*-nitrophenylpyridine (**219**) to β -carboline by heating with ferrous oxalate presents no such difficulties and is easily achieved, although **219** is not very readily available.²⁶⁶ By analogy, it should be possible to obtain a mixture of α - and γ -carboline from 3-*o*-nitrosophenylpyridine (**220**; R = NO₂).



[218]



[219]



[220]

Preliminary experiments²⁶⁷ indicate that α -carboline is the major isomer formed in the reaction. The preparation of a mixture of α - (81.5%) and γ -carboline (18.5%) from 3-*o*-nitrosophenylpyridine

²⁶³ R. A. Abramovitch, K. A. H. Adams, and A. D. Notation, *Can. J. Chem.* **38**, 2152 (1960).

²⁶⁴ H. C. Waterman and D. L. Vivian, *J. Org. Chem.* **14**, 289 (1949).

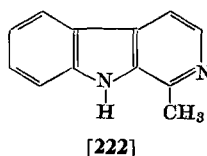
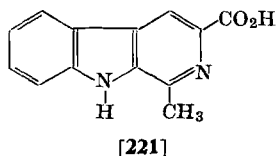
²⁶⁵ R. A. Abramovitch, *Chem. Ind. (London)* 422 (1957).

²⁶⁶ R. A. Abramovitch and J. G. Saha, *J. Chem. Soc.* in press (1964).

²⁶⁷ R. A. Abramovitch and J. G. Saha, unpublished results (1962).

(**220**; R = NO) with triethyl phosphite²⁶⁸ is in agreement with these results.

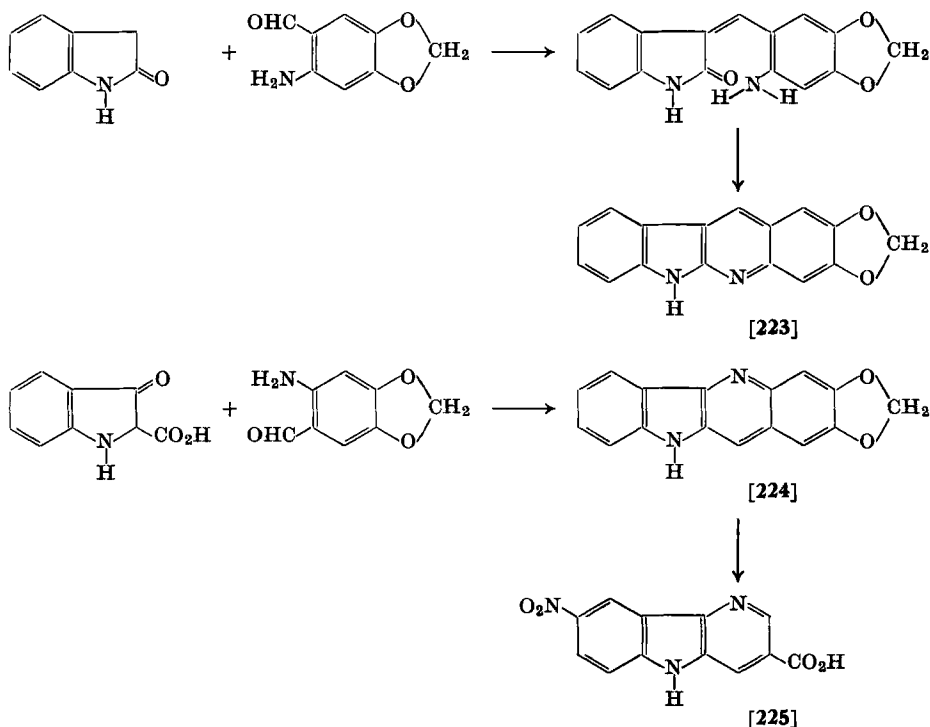
e. *β -Carbolines by Oxidative Cyclization of N_β -Acyltryptophan Derivatives.* When N_β -acyl derivatives of tryptophan are subjected to attempted Bischler-Napieralski cyclization, the corresponding 3,4-dihydro- β -carboline-3-carboxylic acid may be obtained only under very carefully controlled conditions. The usual condensing agents (Section III, C, 1, a) yield tarry products. Reaction of N_β -formyl- and N_β -acetyl-tryptophan at 110–130° with polyphosphoric acid containing phosphorus oxychloride led to ring closure, but this was accompanied by decarboxylation and aromatization giving β -carboline and 1-methyl- β -carboline, respectively, in low yield.²⁰⁶ Reaction of polyphosphoric acid with the ethyl esters of N_β -acetyl- and N_β -phenylacetyl-tryptophan also gave the decarboxylated aromatic products.²⁰⁷ There can be little doubt that the 3,4-dihydro- β -carboline-3-carboxylic acids are intermediates in the reaction. Since 1-methyl-3,4-dihydro- β -carboline-3-carboxylic acid (**138**) has been shown to yield 1-methyl- β -carboline-3-carboxylic acid (**221**), 1-methyl- β -carboline (**222**), 1-methyl-3,4-dihydro- β -carboline (**135**), and 1-methyl-1,2,3,4-tetrahydro- β -carboline (**134**) on high vacuum sublimation at 150–180°, ⁴² it is likely that the low recovery in the cyclization reaction was due to the fact that only one of the products was isolated from the cyclodehydration. A reasonable hypothesis to account for the products obtained from the pyrolysis is a disproportionation with or without simultaneous decarboxylation of 1-methyl-3,4-dihydro- β -carboline-3-carboxylic acid (**138**) to **221** or **222** and 1-methyl-1,2,3,4-tetrahydro- β -carboline (**134**). Decarboxylation of **138** to 1-methyl-3,4-dihydro- β -carboline (**135**) must also occur, but since the latter has been shown to distil without decomposition,¹⁹² this compound cannot give rise to **222** and **134**.



f. *α - and δ -Carboline Derivatives from Oxindole and Indoxyl Derivatives.* Aromatic *o*-aminoaldehydes condense with oxindole and

²⁶⁸ P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.* 42 (1963).

indoxyl derivatives to yield intermediates which can be cyclized to α - (**223**)²⁶⁹⁻²⁷¹ and δ -2,3-benzcarboline derivatives (**224**), respectively, as illustrated.



The quindoline **224** may be prepared by the condensation of indoxyl-2-carboxylic acid with 6-aminopiperonaldehyde in the presence of hydrochloric acid, when decarboxylation and cyclization take place. Nitric acid oxidation of **224** gave an unstable nitrodicarboxylic acid which decarboxylated readily to a nitromonocarboxylic acid formulated as 8-nitro- δ -carboline-3-carboxylic acid (**225**).⁴

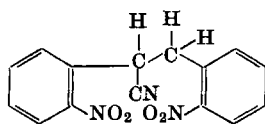
g. Miscellaneous Methods. A variety of methods lead to benzcarboline derivatives. Only a few of the more unusual ones will be

²⁶⁹ J. W. Armit and R. Robinson, *J. Chem. Soc.* **127**, 1604 (1925).

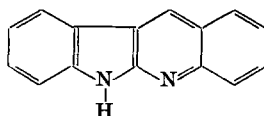
²⁷⁰ J. C. Porter, R. Robinson, and M. Wyler, *J. Chem. Soc.* 620 (1941).

²⁷¹ W. Borsche, M. Wagner-Roemmich, and J. Barthenheier, *Ann. Chem.* **550**, 160 (1942).

mentioned here since the synthesis of such compounds has been very adequately reviewed recently.¹

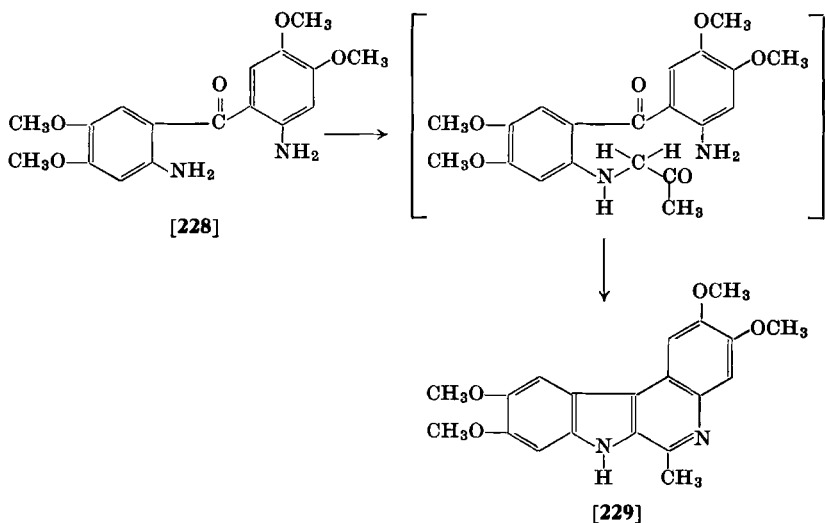


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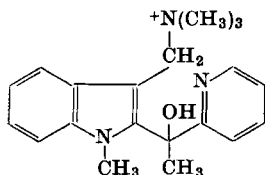


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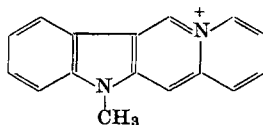
An interesting approach to quinindoline (**227**) is due to Gabriel and Eschenbach²⁷² who found that reductive ring closure of α,β -bis-*o*-nitrophenylpropionic acid with ferrous sulfate and ammonia or of its nitrile (**226**) with alcoholic ammonium sulfide in a sealed tube at 100°



[229]



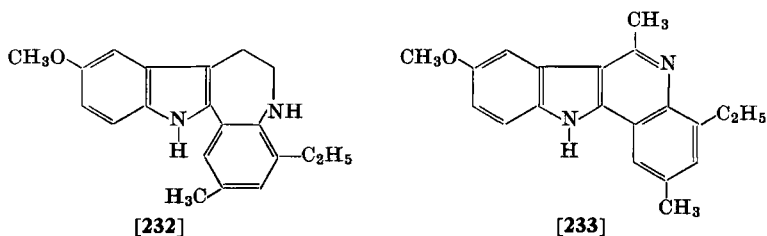
[230]



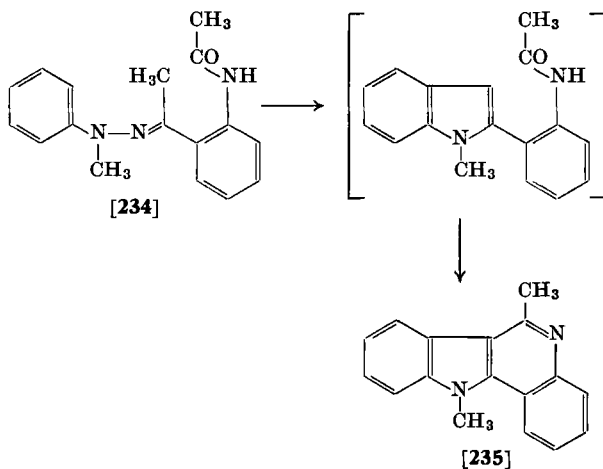
[231]

²⁷² S. Gabriel and G. Eschenbach, *Ber.* **30**, 3017 (1897).

gave **227** directly. The synthesis of the tetramethoxy-4,5-benz- β -carboline (**229**) was effected from aminoveratrone (**228**) by condensation with bromoacetone in acetic acid, when **229** hydrobromide separated.¹³⁵ In an extension of their γ -carboline synthesis, Kebrle and co-workers⁸⁶ prepared **231** by heating the gramine derivative **230** at 100° in 1,2-diethoxyethane solution.

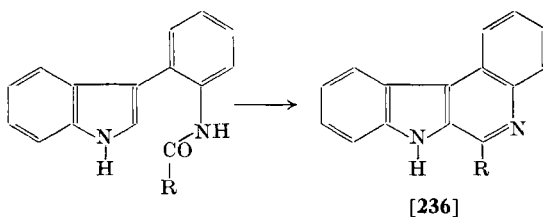


The tetracyclic γ -carboline derivative **233** was obtained *via* an interesting ring contraction when the seven-membered ring compound **232** was heated with selenium.²¹⁶

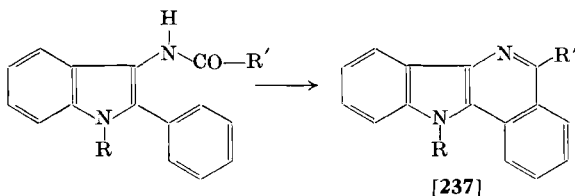


A synthetic approach to the same tetracyclic γ -carboline nucleus (**235**) is the consecutive Fischer indole and Bischler-Napieralski ring closure of *o*-acetamidoacetophenone methylphenylhydrazone (**234**).²⁵⁵

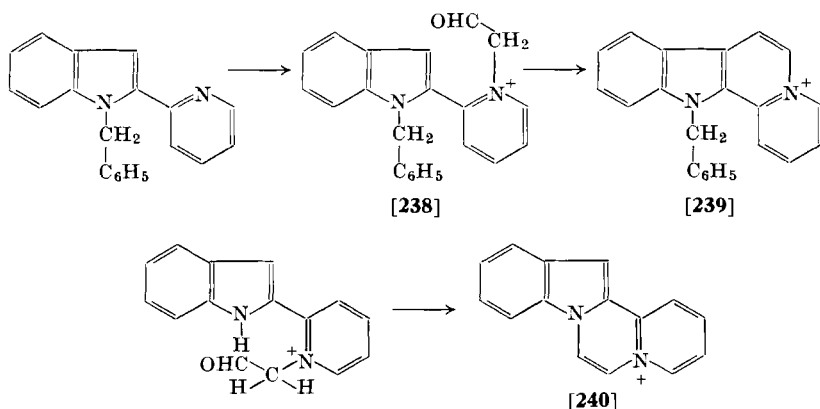
The Bischler-Napieralski reaction has also been used in the synthesis of 3,4-benz- β -carbolines (**236**)²²⁷ and 3,4-benz- δ -carbolines, e.g. **237**



($R = C_6H_5$, $R' = CH_3$)²⁷³ The latter reaction failed,²⁷⁴ or gave poor yields,²⁷³ when the *ind-N* was unsubstituted.



While examining possible approaches to the sempervirine ring system Stevens²⁷⁵ found that when the pyridinium salt **238** was treated with acid a Pomeranz-Fritzsch type cyclization occurred leading to **239**. Without the protective influence of the benzyl group, attack at the indole nitrogen atom took place yielding **240**.



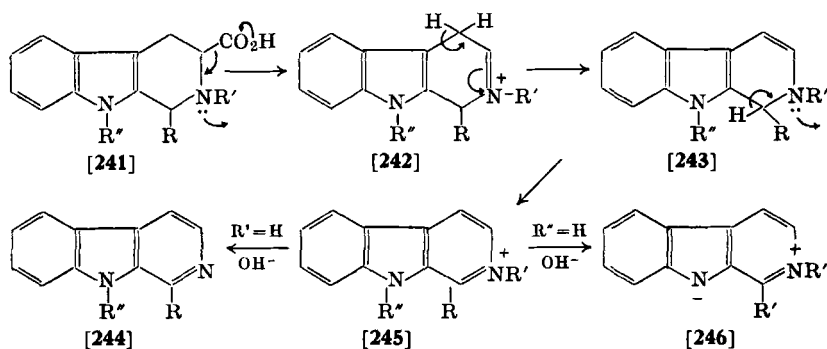
²⁷³ Huang-Hsinmin and F. G. Mann, *J. Chem. Soc.* 2911 (1949).

²⁷⁴ R. Robinson and S. Thornley, *J. Chem. Soc.* 3144 (1962).

²⁷⁵ T. S. Stevens, in "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," p. 19. *Chem. Soc. (London) Spec. Publ. No. 3*, (1955).

2. From Other Oxidation States of the Preformed Ring System

a. *From Tetrahydrocarbolines.* (i) *Oxidative decarboxylation of 1,2,3,4-tetrahydro- β -carboline-3-carboxylic acids.* A reliable method for the synthesis of β -carbolines is the oxidative decarboxylation of the readily available (cf. Section III, 1, a, i) 1,2,3,4-tetrahydro- β -carboline-3-carboxylic acids (**241**). The method was first used by Kermack *et al.*²²¹ who, without isolating the intermediate tetrahydrocarboline-carboxylic acids (**241**), obtained β -carboline (**244**; R = H) and



1-methyl- β -carboline (**244**; R = CH₃) on oxidation of a mixture of tryptophan and formaldehyde or acetaldehyde, respectively, in dilute aqueous solution with acid dichromate. β -Carboline^{40, 62, 63} and 1-methyl-^{44, 50} and 7-methoxy-1-methyl- β -carboline⁴⁴ were later prepared by oxidation of the corresponding tetrahydro- β -carboline-3-carboxylic acids by Robson and his co-workers, and the same procedure has been used for the preparation of numerous other 1-, 5-, 6-, 7-, 8- and 9-substituted β -carbolines.^{41, 43, 45-52} Dichromate oxidation of *pyr-N*-methyl-1,2,3,4-tetrahydro- β -carboline-3-carboxylic acids (**241**; R' = CH₃) yields the corresponding *pyr-N*-methyl- β -carbolinium salts (**245**; R' = CH₃).^{38, 276}

The first stage of the reaction is a special case of the oxidative decarboxylation of amino acids, for which two general mechanistic hypotheses are under discussion.^{277, 278} This is followed by aromatization. A possible mechanism (**241** \rightarrow **242** \rightarrow **243** \rightarrow **245**) has been

²⁷⁶ I.-C. Tung, Y.-H. Huang, C.-C. Wu, and K.-H. Ling, *Tai-wan i-hsueh-hui tsa-chih* **59**, 550 (1960); *Chem. Abstr.* **55**, 13425 (1961).

²⁷⁷ I. D. Spenser, J. C. Crawhall, and D. G. Smyth, *Chem. Ind. (London)* 796 (1956).

²⁷⁸ C. C. Sweeley and E. C. Horning, *J. Am. Chem. Soc.* **79**, 2620 (1957).

suggested⁴³ which takes account of the facts that it has not been possible to isolate intermediates from the reaction⁴⁴ and that tetrahydro- β -carbolines which do not bear a 3-carboxylic acid group cannot be oxidized with dichromate.^{53, 279} One instance of such an oxidation in poor yield has been reported, however.¹⁷¹

(ii) *Oxidation.* Tetrahydro- β -carbolines are aromatized by a number of oxidizing agents. Of these, lead tetraacetate has been applied most consistently. It was Schwarz²⁸⁰ who recognized that tetrahydro-yohimbine, the product obtained earlier by lead tetraacetate oxidation of yohimbine²⁸¹ was in fact an anhydrobase of partial structure **246**. The reaction has been shown to take place irrespective of the configuration at carbon-1 of the carboline moiety¹³⁹ and the method has been used repeatedly,^{121, 141, 282} but it appears to have been applied only to *pyr-N*-alkylated, extended, 1,2,3,4-tetrahydro- β -carboline systems, and not to simple 1,2,3,4-tetrahydro- β -carbolines. Oxidation of the latter has been achieved in individual instances with various oxidizing agents (e.g., choranyl, sulfur in xylene,³⁹ silver carbonate¹²⁴), but no general method has been found and a number of attempts have been unsuccessful.²⁷⁹

(iii) *Dehydrogenation.* β -Carboline derivatives may be obtained from tetrahydro- β -carbolines by zinc dust distillation or high temperature dehydrogenation with selenium or palladium black. Many of the complex indole alkaloids may be degraded, with bond cleavage, to yield simple β -carbolines under these conditions and this approach has become a standard method in structural elucidations. Examples are numerous but outside the scope of this review.

Simple 1,2,3,4-tetrahydro- β -carbolines have been aromatized in this manner. Palladium black at 160–170°^{27, 41, 53, 81, 92} or at higher temperature,²⁸³ palladium–maleic acid in aqueous solution,^{18, 163} and platinum/oxygen⁶ have been used for the purpose. Palladium-on-charcoal in a high-boiling solvent has been used also to aromatize 5,6,7,8-tetrahydro- β -carbolines^{89, 97} and 6,7,8,9-tetrahydro- δ -carboline.⁹⁷

²⁷⁹ H. F. Haynes, E. R. Nelson, and J. R. Price, *Australian J. Sci. Research, Ser. A* **5**, 387 (1952).

²⁸⁰ H. Schwarz, *Experientia* **6**, 330 (1950).

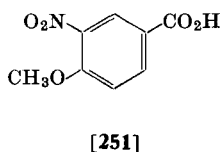
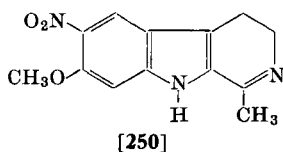
²⁸¹ G. Hahn, E. Kappes, and H. Ludewig, *Ber.* **67**, 686 (1934).

²⁸² M.-M. Janot, R. Goutarel, A. Le Hir, G. Tsatsas, and V. Prelog, *Helv. Chim. Acta* **38**, 1073 (1955).

²⁸³ R. Schwyzler, *Helv. Chim. Acta* **35**, 867 (1952).

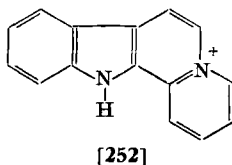
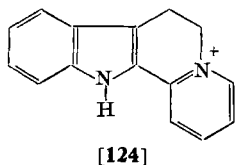
²⁸⁵ M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi, and E. Wenkert, *J. Am. Chem. Soc.* **84**, 622 (1962).

either oxidizes harmaline to harmine^{122, 286} or converts it into 6-nitro-harmaline (**250**),^{287, 288} which may be further oxidized to 6-nitro-harmine.^{288, 289} With concentrated nitric acid at room temperature a mixture of 6-nitroharmaline (**250**) and 4-methoxy-3-nitrobenzoic acid (**251**) is formed.²⁸⁹ Isolation of the latter proves the location of the nitro group at the 6-position of nitroharmaline. Harmaline nitrate gives harmine in high yield when boiled in dilute hydrochloric acid solution.²⁸⁶



Dilute acid permanganate,^{146, 289} acid dichromate,^{65, 210, 290-294} and perbenzoic acid²⁹⁵ have also been employed in the aromatization of 3,4-dihydro- β -carbolines.

Recently Swan has employed tetrachloro-*o*-benzoquinone in the oxidation of the 3,4-dihydro- β -carbolinium cation **124** to the β -carbolinium cation **252**.^{170, 212, 213, 215} Dehydrogenation with palladium black at 175° or at a higher temperature^{5, 53, 92, 134, 181, 186, 204} and with selenium^{184, 296} has also been successfully used for the purpose.



²⁸⁶ S. Elgazin, *Khim. Farm. Prom.* 270 (1933); *Chem. Abstr.* **28**, 3737 (1934).

²⁸⁷ J. Fritzsche, *Ann. Chem.* **68**, 355 (1848).

²⁸⁸ J. Fritzsche, *Ann. Chem.* **88**, 327 (1853).

²⁸⁹ O. Fischer and W. Boesler, *Ber.* **45**, 1930 (1912).

²⁹⁰ J. Fritzsche, *Ann. Chem.* **64**, 360 (1848).

²⁹¹ Y. Asahina, *J. Pharm. Soc. Japan* No. **503**, 1 (1924); *Chem. Abstr.* **18**, 1667 (1924).

²⁹² V. Hasenfratz and R. Sutra, *Compt. Rend.* **182**, 703 (1926).

²⁹³ V. Hasenfratz, *Ann. Chim. (Paris)* [10], **7**, 151 (1927).

²⁹⁴ R. Konovalova, N. Proskurnina, and A. Orekhov, *Arch. Pharm.* **273**, 156 (1935).

²⁹⁵ B. Witkop and H. Fiedler, *Ann. Chem.* **558**, 91 (1947).

²⁹⁶ M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.* **82**, 5941 (1960).

1-Methyl-3,4-dihydro- β -carboline-3-carboxylic acid has been reported to undergo photochemical²⁰⁸ and pyrolytic⁴² oxidation to yield a mixture containing 1-methyl- β -carboline and 1-methyl- β -carboline-3-carboxylic acid. The methyl ester of this 3,4-dihydro- β -carboline acid appears to be oxidized to methyl 1-methyl- β -carboline-3-carboxylate on alumina chromatography.⁸⁵

A number of unsuccessful attempts to dehydrogenate dihydro- β -carbolines have been reported.^{188, 212}

c. *From Oxodihydro- and Oxotetrahydro-carbolines.* A few isolated examples of such conversions have been reported. 1-Oxo-1,2,3,4-tetrahydro- β -carboline,²³¹ 9-methyl-1-oxo-1,2-dihydro- β -carboline,²²¹ and some related compounds²²⁷ have been converted in poor yield into the corresponding β -carbolines by distillation with zinc dust in a stream of hydrogen. Treatment of 1-oxo-1,2-dihydro- β -carboline-3-carboxylic acid with phosphorus pentachloride, followed by phosphorus-hydriodic acid reduction of the resulting 1-chloro- β -carboline-3-carboxylic acid, led to β -carboline-3-carboxylic acid.²²⁶ The only method which promises to be of general application, treatment of a 1-oxo-1,2,3,4-tetrahydro- β -carboline with phosphorus oxychloride under vigorous conditions,^{175, 220} is referred to in Section III, C, 2, c.

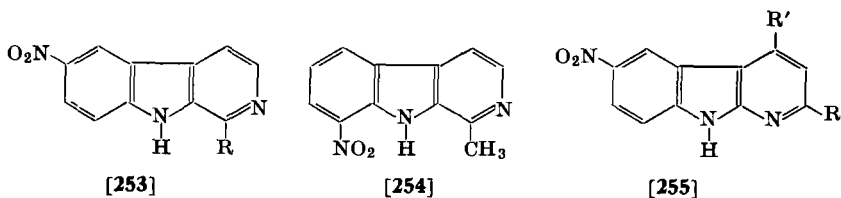
IV. Reactions of the Carbolines

A. REACTIONS OF THE FULLY AROMATIC CARBOLINES

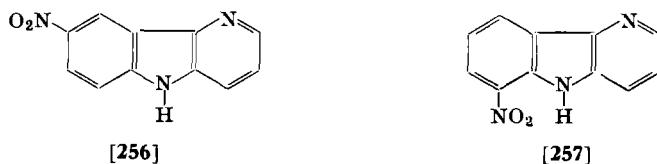
1. Substitutions at Carbon

Relatively little is known concerning the substitution reactions of the carbolines. The most studied reaction is that of nitration. Nitration of 1-methyl- β -carboline gave two mononitro derivatives. The higher-melting isomer, which was formed predominantly (57% yield), was shown to be 6-nitro-1-methyl- β -carboline (**253**; R = CH₃) by its conversion into 6-bromo-1-methyl- β -carboline; the latter was synthesized unambiguously from 5-bromotryptophan and acetaldehyde. The lower melting isomer, recovered in 20% yield, was presumed to be the 8-nitro derivative (**254**), although this was not established.⁵⁰ Nitration of β -carboline with concentrated nitric acid at 35° has been reported²⁰⁷ to yield 6-nitro- β -carboline (**253**; R = H) as the sole product. Only the 6-nitro derivatives (**255**) were isolated on nitration

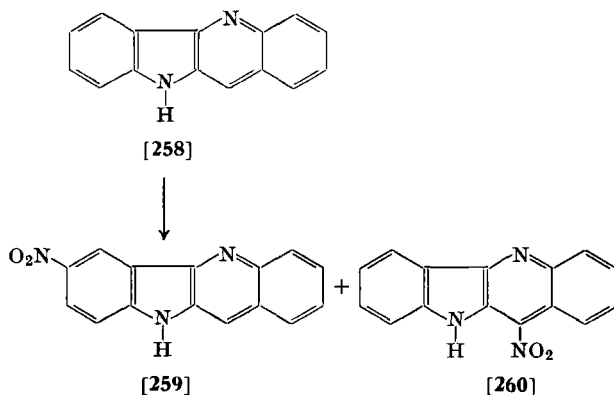
²⁰⁷ I.-C. Tung, *Tai-wan i-hsueh-hui tsa-chih* **59**, 889 (1960); *Chem. Abstr.* **55**, 22314 (1961).



of α -carboline and its 2- and 4-methyl derivatives.²⁹⁸ The nitration of δ -carboline has been found⁹⁷ to give two isomeric mononitro derivatives. The main (and higher-melting) product was shown to be the 8-nitro derivative (256) by its reduction to the corresponding amine, which gave a positive test for a *p*-phenylenediamine having a primary



amino group.²⁹⁹ By analogy with the nitration of 1-methyl- β -carboline and carbazole, the lower-melting isomer was assumed to be 6-nitro- δ -carboline (257). Infrared and ultraviolet absorption data support this assignment. The nitration of quindoline (258), however, is reported to give 7-nitroquindoline (259) as the major product together with

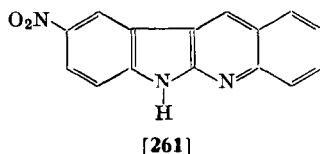


²⁹⁸ R. R. Burtner, U.S. Patent 2,690,441 (1954); *Chem. Abstr.* **49**, 13297 (1955),

²⁹⁹ F. Feigl, "Spot Tests, Organic Applications." Vol. II, p. 296. Elsevier, Amsterdam, 1954.

11-nitroquindoline (**260**) as the minor one.³⁰⁰ That the second product was indeed **260** was established by its reduction to the corresponding amine, which was also obtained by a Curtius reaction on the hydrazide of quindoline-11-carboxylic acid. The structure of this carboxylic acid is unambiguous since it was prepared by the reaction of indoxyl with isatin in alkaline solution.³⁰¹ The formation of **260** is unexpected since it represents nitration under relatively mild conditions of a pyridinium ring—admittedly bearing an activating 3-imino group—in preference to attack at the relatively activated 9-position. It seems more likely that this product arises from the rearrangement of an intermediate *ind-N*-nitramine; the intervention of free-radical intermediates in this type of rearrangement has recently been suggested.³⁰² The possibility that the minor product from the nitration of δ -carboline is actually the 4-nitro derivative has not been eliminated.

Nitration of quinindoline gave the expected 9-nitro derivative (**261**).²⁵¹ A single mononitro compound was formed from the 3,4-dihydro- β -carboline, harmaline^{287-289, 294}; this was 6-nitroharmaline, since on oxidation it yielded 3-nitro-4-methoxybenzoic acid.



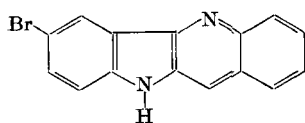
The bromination of 7-methoxy-1-methyl- β -carboline (harmine) was studied by Fischer.¹²² He obtained a compound, $C_{13}H_{12}Br_4N_2O$, which he called tetrabromoharmine, by the action of bromine water on a dilute sulfuric acid solution of harmine. The bromination of harmine was reinvestigated by Hasenfratz,²⁹³ who found that two products (both hydrobromides) could be isolated when harmine was treated with bromine in aqueous acetic acid. The major component formed colorless needles and was called bromoharmine hydrobromide (free base: colorless needles, m.p. 275°), while the product obtained in lesser amount was a canary-yellow dihydrate which was named "isobromoharmine hydrobromide" (free base: colorless needles, m.p.

³⁰⁰ S. J. Holt and V. Petrow, *J. Chem. Soc.* 607 (1947).

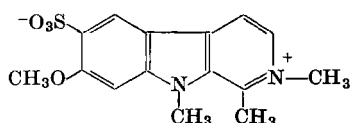
³⁰¹ F. Fichter and F. Rohner, *Ber.* **43**, 3489 (1910).

³⁰² W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, J. T. Golden, and H. S. White, *J. Am. Chem. Soc.* **83**, 2024 (1961); W. N. White and J. T. Golden, *Chem. Ind. (London)* 138 (1962).

203°). Isobromoharmine was also obtained by the chromic acid oxidation of bromoharmaline (formed in the reaction of harmaline with bromine in aqueous acetic acid). Hasenfratz suggested that both of these products were *C*-bromo compounds but did not propose structures for them. He found, however, that if isobromoharmine was heated at 160° for 8 hours in a sealed tube with dilute hydrochloric acid it was converted irreversibly into bromoharmine. Since aromatic *C*-chlorination and *C*-bromination are generally believed to be irreversible³⁰³ and rearrangement of aromatic *C*-chloro and *C*-bromo groups has been shown to take place only when a vigorous catalyst, e.g. AlCl_3 or AlBr_3 , is used,³⁰⁴ it seems more likely that "isobromoharmine" is actually an *ind-N*-bromo derivative and that the bromine atom in bromoharmine is linked to carbon-6. The structure of "isobromoharmine" may well bear re-examination. More recently, Barković and Bican³⁰⁵ have confirmed that with one molar equivalent of bromine in sulfuric acid harmine gives the same bromoharmine as was isolated by Hasenfratz. Addition of a second mole of bromine resulted in the formation of a dibromoharmine, m.p. 209–211°, which had also been obtained by Hasenfratz. These authors suggested that the "tetrabromoharmine" isolated by Fischer¹²² was actually the dihydrobromide, $\text{C}_{13}\text{H}_{10}\text{Br}_2\text{N}_2\text{O} \cdot 2\text{HBr}$, of the above dibromoharmine. This seems rather unlikely since Fischer showed that treatment of this "tetrabromoharmine" with sulfur trioxide or with boiling alcohol caused it to revert to harmine itself, whereas Hasenfratz²⁹³ found that it gave bromoharmine hydrobromide on boiling with water. It appears more probable, therefore, that Fischer's "tetrabromoharmine" was a perbromide hydrobromide of harmine or a complex with molecular bromine.



[262]



[263]

³⁰³ P. B. D. de La Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation," p. 114, Butterworths, London, 1959.

³⁰⁴ G. A. Olah, W. S. Tolgyesi, and R. E. A. Dear, *J. Org. Chem.* **27**, 3441, 3449, 3455, 3464 (1962).

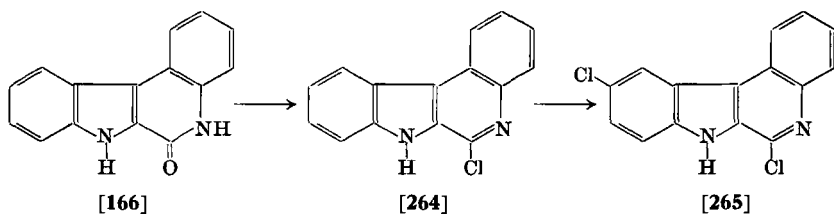
³⁰⁵ D. Barković and T. Bican, *Arhiv Kemi* **20**, 135 (1948); *Chem. Abstr.* **44**, 5884 (1950).

Bromination of quindoline (258) gives 7-bromoquindoline (262).^{300, 301}

The sulfonation of harmine was studied by a number of workers.^{150, 293, 306} A sulfonic acid was obtained which was nonbasic and which regenerated harmine on treatment with boiling hydrochloric acid. The assumption that the compound must be formulated as an *ind-N*-sulfonic acid to explain these properties^{293, 306} is unnecessary. A *C*-substituted 1-methyl- β -carboline sulfonic acid would undoubtedly be zwitterionic and would also undergo desulfonation readily. Indeed, Kermack *et al.*¹²⁹ found that *N,N'*-dimethylharminium chloride, in which *N*-substitution is no longer possible, was sulfonated similarly to give a compound which they formulated as 263. They rejected their earlier tentative suggestion¹⁵⁰ that *N*-sulfonation of harmine had occurred and postulated that, in fact, sulfonation of the benzene ring had taken place.^{306a}

It is interesting to note that whereas 7-methoxy-1-methyl-1,2,3,4-tetrahydro- β -carboline condenses with diazobenzenesulfonic acid to give an azo compound (presumably the 6-arylazo derivative)¹⁵⁰ and 7-methoxy-1-methyl-3,4-dihydro- β -carboline gives a bisazo compound,^{150, 289} none of the fully aromatic β -carboline derivatives studied by Perkin and Robinson¹⁵⁰ underwent azo-coupling.

1,2-Dihydro-1-oxo-3,4-benz- β -carboline (166) reacted with phosphorus oxychloride and one mole of phosphorus pentachloride at 110° to give 1-chloro-3,4-benz- β -carboline (264). When, however, more than one mole of phosphorus pentachloride was used 265 was obtained, presumably by chlorination of 264.³⁰⁷ This chlorinating action of phosphorus pentachloride is analogous to that observed when an



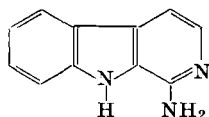
³⁰⁶ O. Fischer and C. Buck, *Ber.* **38**, 329 (1905).

^{306a} Hasenfratz²⁹³ was clearly unaware of this work by Kermack *et al.*¹²⁹ since as late as 1927 he still formulated the sulfonic acid derivatives of harmine, harmaline, harmol, and harmalol as *N*-sulfonic acids.

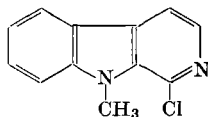
³⁰⁷ W. O. Kermack and W. Tebrich, *J. Chem. Soc.* 314 (1940).

excess of phosphorus pentachloride in chlorobenzene acts on certain diphenylaminocarboxylic acids.³⁰⁸

The action of nucleophilic reagents on the carbolines has been investigated only briefly. 1-Amino- β -carboline (**266**) was obtained by the action of amide ion on β -carboline.⁶² This is the product expected on the basis of the order of the ground-state π -electron densities as calculated by Paoloni.³⁰⁹ The fact that starting material was recovered



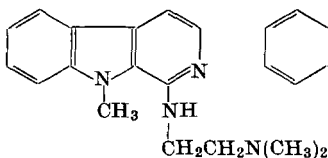
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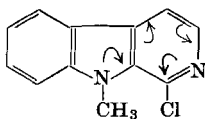
[267]

from the reaction of phenyllithium with δ -carboline was attributed⁹⁷ to the formation of an insoluble *ind-N*-lithium salt. A small amount of phenylated product, presumably 2-phenyl-5-methyl- δ -carboline, was obtained, however, by treating *ind-N*-methyl- δ -carboline with phenyllithium⁹⁷; unfortunately, insufficient quantities were available to permit definite characterization.

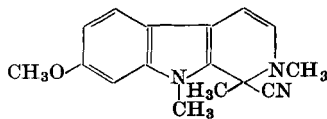
1-Chloro-9-methyl- β -carboline (**267**) did not react with the Grignard reagent,¹²⁹ and it was found that the chlorine atom in **267** was less susceptible to nucleophilic attack than was that in 2-chloropyridine and 2-chloroquinoline.³⁰⁷ Thus, condensation with β -dimethylaminoethylamine proceeded only with difficulty to give a small amount of **268**. The *pyr-N*-methosulfate reacts much more readily, as expected.



[268]



[269]



[270]

The lowered reactivity of the 1-halogen atom in **267** is not unexpected in view of the fact that electron donation by the indole-nitrogen atom as in **269** would reduce the susceptibility of carbon-1 to nucleophilic

³⁰⁸ R. R. Goodall and W. O. Kermack, *J. Chem. Soc.* 1163 (1936).

³⁰⁹ L. Paoloni, *Gazz. Chim. Ital.* **90**, 1530 (1960).

attack. This also explains the findings that β -carboline does not form Reissert compounds,³¹⁰ that 6-nitroharmine does not form an adduct with cyanide ion,²⁸⁸ and that the cyanide adduct, presumably **270**, derived from a 1,2-dimethyl-7-methoxy- β -carbolinium salt is very unstable.¹⁵¹

2. Reactions at Nitrogen

The alkylation of carboline derivatives has been repeatedly studied. The first quaternary *N*-alkyl carbolinium salts to be described were those prepared in connection with the elucidation of the structure of harmine (methiodide,^{146, 311} methochloride, and methosulfate¹⁵⁰). Other β -carbolinium salts were subsequently prepared in connection with systematic studies of the site of alkylation^{3, 129, 312, 313} and of the structure and the course of further alkylation of the anhydro-bases derived from 2-alkyl- β -carbolinium salts (*vide infra*), as well as in the search for pharmaceuticals.^{131, 314, 315}

Alkylation takes an entirely unexceptional course. The nitrogen atom of the π -excessive five-membered ring of the indole nucleus resists alkylation. *ind-N*-Alkylation with alkyl halides can be achieved only after forcing deprotonation with, for example, sodamide, potassium amide or ethoxide. In this manner α -,²⁵⁴ β -,^{43, 126, 148, 314, 316-320} and γ -carboline derivatives²⁵⁴ have been converted into the corresponding *ind-N*-alkyl derivatives. δ -Carbolines, on the other hand, resisted all attempts at *ind-N*-methylation.²⁶³

ind-N-Substitution of β -carboline and its *C*-substituted derivatives can also be brought about by Michael addition of the base and acryl-

³¹⁰ I. W. Elliott, *J. Am. Chem. Soc.* **77**, 4408 (1955).

³¹¹ O. Fischer and E. Täuber, *Ber.* **18**, 400 (1885).

³¹² R. Kononova and A. Orekhov, *Arch. Pharm.* **272**, 748 (1934).

³¹³ V. V. S. Iyer and R. Robinson, *J. Chem. Soc.* 1635 (1934).

³¹⁴ A. P. Gray, E. E. Spinner, D. C. Schlieper, and C. J. Cavallito, *J. Am. Chem. Soc.* **77**, 3533 (1955).

³¹⁵ N. F. Kucherova, V. P. Evdakov, and N. K. Kochetkov, *J. Gen. Chem. USSR (Eng. Transl.)* **28**, 2005 (1958).

³¹⁶ M. J. S. Dewar, *J. Chem. Soc.* 619 (1944).

³¹⁷ D. Mukherji, R. Robinson, and E. Schlittler, *Experientia* **5**, 215 (1949).

³¹⁸ F. A. L. Anet, D. Chakravarti, R. Robinson, and E. Schlittler, *J. Chem. Soc.* 1242 (1954).

³¹⁹ P. Karrer and H. Müller, *J. Org. Chem.* **22**, 1433 (1957).

³²⁰ L. Zhelyazkov, N. Bikova, and E. Petkova, *Farmatsiya (Sofia)* **7**, 29 (1957); *Chem. Abstr.* **54**, 10992 (1960).

onitrile^{321, 322} or ethyl acrylate³²³ in the presence of benzyltrimethylammonium hydroxide (Triton B). One instance of *ind-N*-methylation of a β -carboline derivative with diazomethane has been recorded.²²⁶

The basic nitrogen of the six-membered hetero ring in α -,^{6, 43, 136, 269, 314} β -,^{3, 129, 146, 311-313, 323*} γ -,¹⁰⁴ and δ -carboline derivatives^{263, 273} quaternizes readily with alkyl halides or sulfates to yield the corresponding *pyr-N*-alkylcarbolinium salts.

Further alkylation of the anhydro-bases derived, by treatment with strong base, from quaternary 1-alkyl- α -, 2-alkyl- β -, 2-alkyl- γ -, and 1-alkyl- δ -carbolinium salts takes place at the indole nitrogen which in the anhydro-bases is a center of high electron density (see Section VI).

The stepwise alkylation of a β -carboline derivative at two different sites was first demonstrated by Kermack *et al.*¹²⁹ Treatment with *n*-propyl iodide of the anhydro-base **273** derived from harmine methiodide (**272**) gave a product (**274**) which was different from, but isomeric with, the product (**277**) obtained by reaction with methyl iodide of the anhydro-base **276** derived from harmine *n*-propiodide (**275**). Similar isomeric products were obtained by stepwise alkylation of 7-methoxy- and 7-methoxy-1-styryl- β -carboline with methyl and ethyl iodide.³¹² Final proof of the positions of the alkyl groups was supplied by Leonard and Elderfield,⁴¹ who prepared 9-ethyl- β -carboline by unequivocal synthesis and found its ethiodide to be identical with the quaternary salt derived from β -carboline by quaternization with ethyl iodide, conversion of the product into the anhydro-base, and treatment of the latter with ethyl iodide. A similar sequence of reactions had been carried out earlier in the 3,4-benz- β -carboline series³ and has since been repeated with other derivatives.^{43, 46} Such a stepwise alkylation sequence was used in a most ingenious manner to build a pentacyclic system⁷⁹ (see Section V).

The products of these double-alkylation sequences in the β -carboline series, 2,9-dialkyl- β -carbolinium salts, react with base to yield the corresponding quaternary hydroxides. Pyrolysis of the salts leads to dealkylation at the *pyr-N* with the production of the corresponding *ind-N*-alkyl- β -carbolines.^{45, 46, 313}

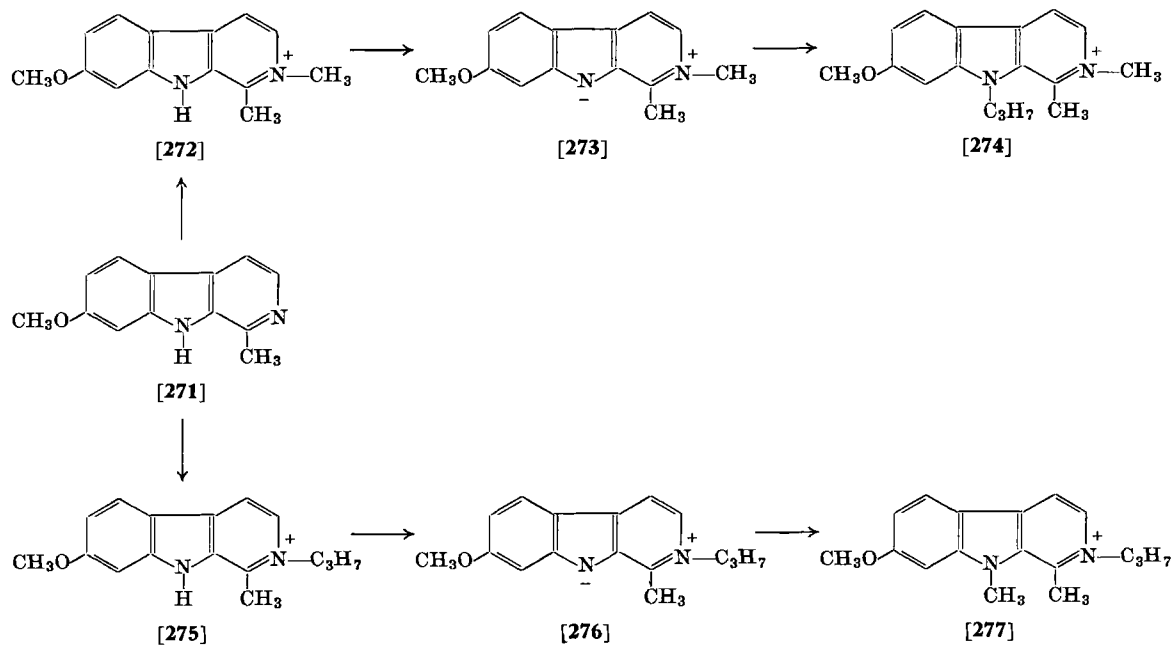
In the α -,^{6, 136} γ -,^{104, 255} and δ -carboline²⁶³ series stepwise alkylation

³²¹ W. Voegtli, U.S. Patent 2,850,501 (1959); *Chem. Abstr.* **53**, 12309 (1959).

³²² A. L. Mndzhoyan and S. G. Agbalyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **13**, 297 (1960); *Chem. Abstr.* **55**, 18788 (1961).

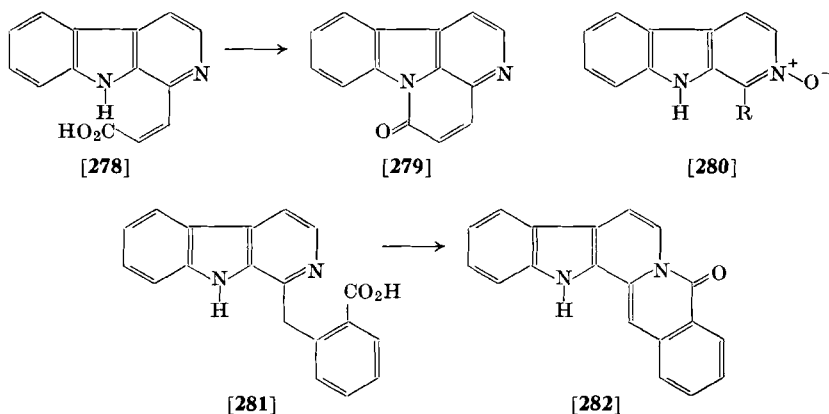
³²³ R. A. Robinson, U.S. Patent 3,015,660 (1959); *Chem. Abstr.* **56**, 8718 (1962).

^{323*} G. Cerbai and G. F. DiPaco, *Farmaco, Ed. Sci.* **18**, 721 (1963); *Chem. Abstr.* **60**, 1807 (1964).



takes an analogous course. Pyrolytic dealkylation of the resulting dialkylcarbolinium salts also yields the corresponding *ind-N*-substituted carbolines.²⁶³

Acylation of β -carboline under Schotten-Baumann conditions yields the *ind-N*-acyl derivative.^{63, 194} An intramolecular acylation of the *cis*-isomer of **278** to yield **279** has been carried out^{279, 296} (see Section V). On the other hand, intramolecular acylation at the *pyr-N* of a β -carboline, in the instance of the spontaneous cyclization of **281** to the pentacyclic compound **282**, has been reported.³²⁴



Reaction of β -carboline derivatives with hydrogen peroxide²⁷⁹ or perbenzoic acid²⁹⁵ and of δ -carboline with peracetic acid²⁶² yields the corresponding *pyr-N*-oxide (e.g. **280**).

3. Reduction, Oxidation, and Ring Cleavage

The reductive (Sections III, A, 2, a and III, C, 2, a) and oxidative transformations (Section III, D, 2, a) of fully aromatic carboline derivatives are discussed in the context of the interconversion of the oxidation states. *N*-Oxide formation is referred to in Section IV, A, 2.

In the course of structural investigations of a number of β -carboline alkaloids, reactions leading to ring cleavage have been encountered.

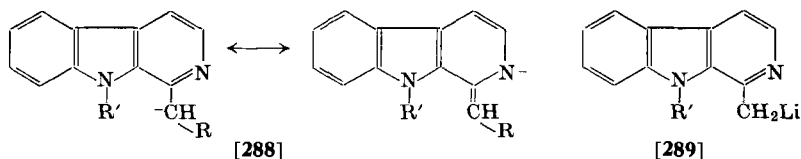
Oxidation of harmine (**271**)^{122, 150, 293, 306, 311, 325} and of harmaline (**122**)¹²² leads, by cleavage of the benzene ring, to harminic acid (**283**; R = CH₃) which undergoes pyrolytic decarboxylation to apoharmine monocarboxylic acid and thence to apoharmine (**284**).

³²⁴ R. B. Woodward and B. Witkop, *J. Am. Chem. Soc.* **70**, 2409 (1948).

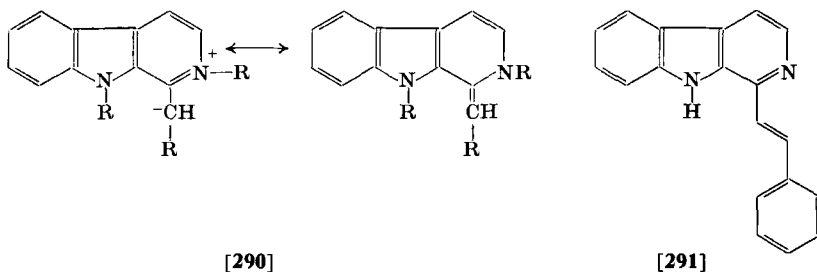
³²⁵ V. Hasenfratz, *Compt. Rend.* **154**, 704 (1912).

4. The Reactivity of 1-Substituents

The reactivity of the 1-methyl group and of corresponding positions (i.e., α -carbon atoms) in other 1-alkyl- β -carbolines, analogous to that in α -picoline, quinaldine, and isoquinaldine, is due to the acidity of this center. Deprotonation yields a resonance-stabilized anion (**288**) which reacts readily with electrophilic reagents. Metallation with phenyllithium of the 1-methyl group of a 1-methyl- β -carboline derivative in which the indole nitrogen is protected, first described by Woodward



and McLamore,³³² leads to the lithium adduct **289** which reacts with carbonyl compounds to yield alcohols^{296, 332, 333} and may be alkylated with alkyl halides.³¹⁹ Use of the anion in an attempted Michael addition was unsuccessful.³³⁴ Other synthetic possibilities have not been explored, but it is likely that quaternary carbolinium ions will yield the deprotonated species **290** and should be suitable starting materials for reactions of this type.



The reactivity of 1-methyl groups is further exemplified by their facile reaction with aromatic aldehydes^{133, 147, 221, 312, 326, 335, 335a} to give 1-styryl derivatives (**291**). The reactivity of the α -carbon in a

³³² R. B. Woodward and W. M. McLamore, *J. Am. Chem. Soc.* **71**, 379 (1949).

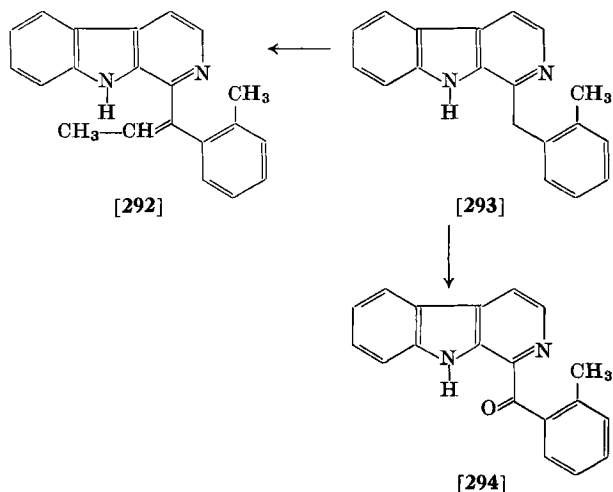
³³³ C. F. Huebner, H. B. MacPhillamy, A. F. St. André, and E. Schlittler, *J. Am. Chem. Soc.* **77**, 472 (1955).

³³⁴ E. E. van Tamelen, D. L. Hughes, and C. W. Taylor, *J. Am. Chem. Soc.* **78**, 4625 (1956).

³³⁵ W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **101**, 1775 (1912).

^{335a} L. V. Khazhaky, A. V. Mkhitarian, G. L. Grigoryan, and G. T. Takevosyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **16**, 181 (1963); *Chem. Abstr.* **59**, 14036 (1963).

1-benzyl derivative [e.g. yobyryne (**293**)] is further enhanced, yielding stable derivatives (**292**) with aliphatic aldehydes.³³⁶ The analogous 2-methyl group in a quaternary 1,2-dimethyl-3,4-benzo- δ -carbolinium salt has been condensed with aromatic aldehydes³³⁷ and nitroso compounds.²⁷³



Another manifestation of the reactivity at this center is the ease of oxidation. Chromic oxide³³⁸ and selenium dioxide³³⁹ convert yobyryne into yobyryne (**294**). 3,4-Dihydroxyobyryne is oxidized to yobyryne by atmospheric oxygen.¹⁸⁶ 7-Methoxyobyryne, on the other hand, failed to oxidize to the corresponding yobyryne.³⁴⁰ Similarly, oxidation with selenium dioxide of 7-methoxy-1-methyl- β -carboline-1-carboxaldehyde was difficult.³⁴¹ 6,7-Dimethoxyobyryne, however, is formed by spontaneous air oxidation of 6,7-dimethoxyobyryne.¹³⁴

1-Styryl- β -carboline (**291**) and quaternary 1-styryl- β -carbolinium salts are readily oxidized by acid permanganate to the corresponding β -carboline-1-carboxylic acids.^{133, 221, 335}

³³⁶ B. Witkop, *Ann. Chem.* **554**, 83 (1943).

³³⁷ R. H. Glauret and F. G. Mann, *J. Chem. Soc.* 2135 (1952).

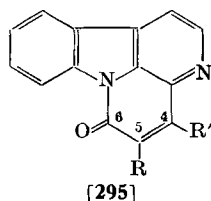
³³⁸ C. Scholz, *Helv. Chim. Acta* **18**, 923 (1935).

³³⁹ B. Witkop, *Ann. Chem.* **554**, 127 (1943).

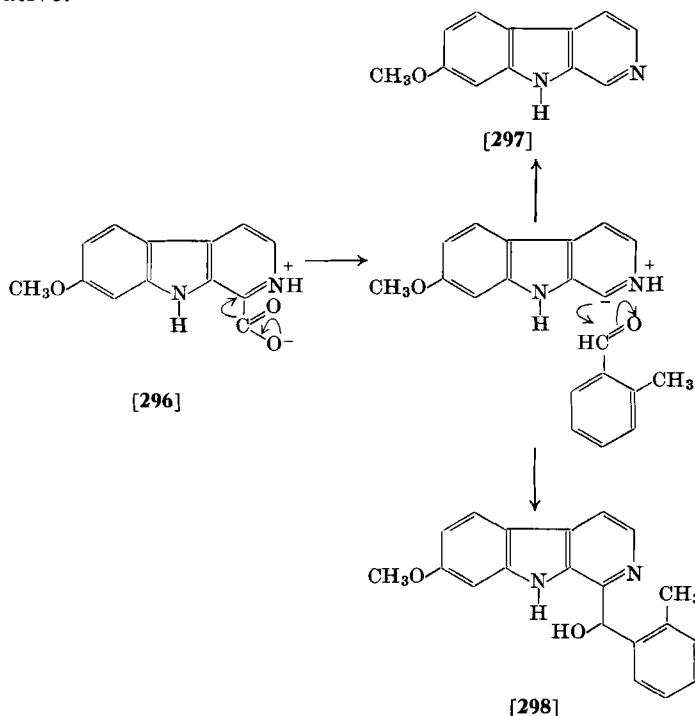
³⁴⁰ L. Dorfmann, A. Furlenmeyer, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzler, and A. F. St. André, *Helv. Chim. Acta* **37**, 59 (1954).

³⁴¹ A. L. Mndzhoyan and S. G. Agbalyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **13**, 207 (1960); *Chem. Abstr.* **55**, 12438 (1961).

Similarly, permanganate oxidation of a number of naturally occurring canthin-6-one derivatives (**295**) leads to β -carboline-1-carboxylic acid^{279, 342, 343} or its methyl ester.³⁴⁴ A β -carboline-1-carboxylic acid



has also been obtained by potash fusion of the corresponding 1-methyl derivative.^{122, 221}



³⁴² E. R. Nelson and J. R. Price, *Australian J. Sci. Research, Series A* **5**, 563 (1952).

³⁴³ E. R. Nelson and J. R. Price, *Australian J. Sci. Research, Series A* **5**, 768 (1952).

³⁴⁴ N. Inamoto, S. Masuda, O. Simamura, and T. Tsuyuki, *Bull. Chem. Soc. Japan* **34**, 888 (1961).

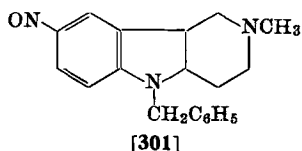
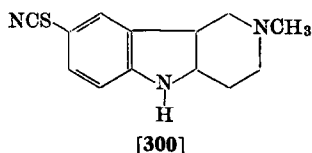
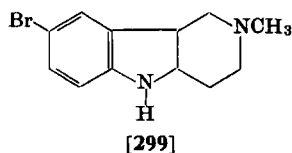
As expected for *N*-heterocyclic α -carboxylic acids, β -carboline-1-carboxylic acids decarboxylate readily on heating^{127, 132, 221, 335} and undergo the Hammick reaction.³⁴⁵ When 7-methoxy- β -carboline-1-carboxylic acid (**296**) was briefly heated in pyridine with *o*-tolualdehyde, the "Hammick" product (**298**) was isolated, together with 7-methoxy- β -carboline (**297**).³⁴⁰

B. REACTIONS OF CARBOLINES IN OTHER OXIDATION STATES

1. At Carbon

Most of the substitution reactions of di-, tetra, and hexa-hydro-carbolines and of their oxo derivatives are similar to those of the parent indole or indolenine derivatives. Nitration and bromination of harmaline (1-methyl-3,4-dihydro- β -carboline) are referred to in Section IV, A, 1. Sulfonation and azo-coupling¹⁵⁰ proceed as expected for indole derivatives. The preparation of chlorinated and iodinated derivatives of 6-nitroharmaline has been reported,³⁴⁶ but their structures have not been established.

2-Methyl-1,2,3,4,4a,9b-hexahydro- γ -carboline (**93**) readily undergoes bromination with bromine in acetic acid to give the 8-bromo derivatives (**299**) and thiocyanation with potassium thiocyanate in methanol containing bromine and sodium bromide to give the 8-thiocyanato derivative (**300**). If the indolenine nitrogen atom is protected by a benzyl group, nitrosation can take place at carbon-8 to give **301** which can be reduced catalytically to the primary amine in quantitative yield.¹⁸⁰

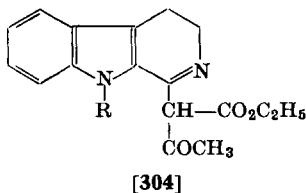
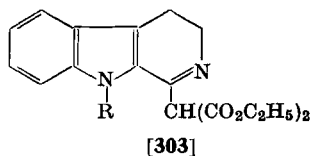
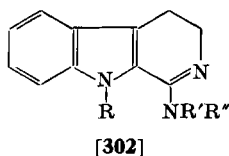


³⁴⁵ P. Dyson and D. L. Hammick, *J. Chem. Soc.* 1724 (1937); M. R. F. Ashworth, R. P. Daffern, and D. L. Hammick, *J. Chem. Soc.* 809 (1939).

³⁴⁶ J. Fritzsche, *Ann. Chem.* **92**, 328 (1854).

1,2-Dihydro-9-methyl-1-oxo- β -carboline¹²⁹ and its 6-methoxy derivative³⁰⁷ and 1,2-dihydro-1-oxo- β -carboline-3-carboxylic acid²²⁶ were converted into the 1-chloro compounds quite readily under carefully controlled conditions, whereas the cyclic amide group was unreactive towards phosphorus pentachloride under the same conditions both in 1,2,3,4-tetrahydro-1-oxo- β -carboline and its 9-methyl derivative, starting material being recovered.¹⁷³

The conversion of 1-oxo-1,2,3,4-tetrahydro- β -carbolines into 1-alkoxy- and 1-alkylamino-3,4-dihydro- β -carbolines is mentioned in Section III, C, 2, c.



1-Alkoxy-9-alkyl-3,4-dihydro- β -carbolines (**152**) readily undergo substitution of the alkoxy group by nucleophilic reagents such as amines, diethyl malonate, and ethyl acetoacetate to give compounds of the type **302**, **303**, and **304**.³⁴⁷ A similar facile nucleophilic substitution of a 1-alkoxy group is involved in the smooth reaction of 1-methoxy-3,4-dihydro- β -carboline with anthranilic acid in boiling methanol to give rutaecarpine (**111**) in good yield.³⁴⁸

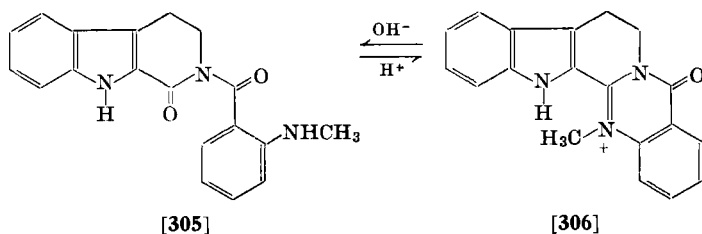
The interesting reversible cyclization **305** \rightleftharpoons **306** should be referred to in this context.^{175, 349, 350}

³⁴⁷ H. Henecka, R. Lorenz, and H. Timmler, German Patent 1,044,818 (1958); *Chem. Abstr.* **55**, 3622 (1961).

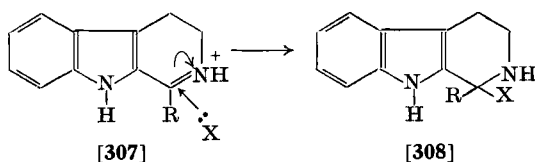
³⁴⁸ S. Petersen and E. Tietze, *Ann. Chem.* **623**, 166 (1959).

³⁴⁹ I. J. Pachter, R. F. Raffauf, G. E. Ulyot, and O. Ribeiro, *J. Am. Chem. Soc.* **82**, 5187 (1960).

³⁵⁰ I. J. Pachter and G. Suld, *J. Org. Chem.* **25**, 1680 (1960).

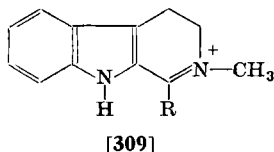


Finally, mention should be made of the addition of nucleophilic reagents to the 1-position of 3,4-dihydro- β -carbolines. Cyanide has been reported to yield adducts with harmaline,^{351, 352} 6-nitroharmaline,³⁵² and 2-methylharmalinium salt¹⁵¹; similarly, hydroxylamine forms adducts with harmaline,¹⁴⁷ 3,4-dihydro- β -carboline¹⁹² (**307**; R = H), and 1-phenyl-3,4-dihydro- β -carboline (**307**; R = C₆H₅).³⁵³ Only in one case was the structure of the adduct rigorously established, but it would appear most likely that these adducts are 1-cyano- or 1-hydroxylamino-1,2,3,4-tetrahydro- β -carboline derivatives (**308**).



2. Reactions at Nitrogen

Quaternization with alkyl halides of 3,4-dihydro- β -carboline and its derivatives takes place at the *pyr-N*. Quaternary 3,4-dihydro- β -carbolinium salts (**309**) derived from harmaline,^{146, 147, 150, 311, 312} 3,4-dihydro- β -carboline,¹⁹² 6-methoxy-3,4-dihydro- β -carboline,¹⁷⁵ and 1-methyl-3,4-dihydro- β -carboline³⁵⁴ have been described. Further



³⁵¹ J. Fritzsche, *Ann. Chem.* **68**, 351 (1848).

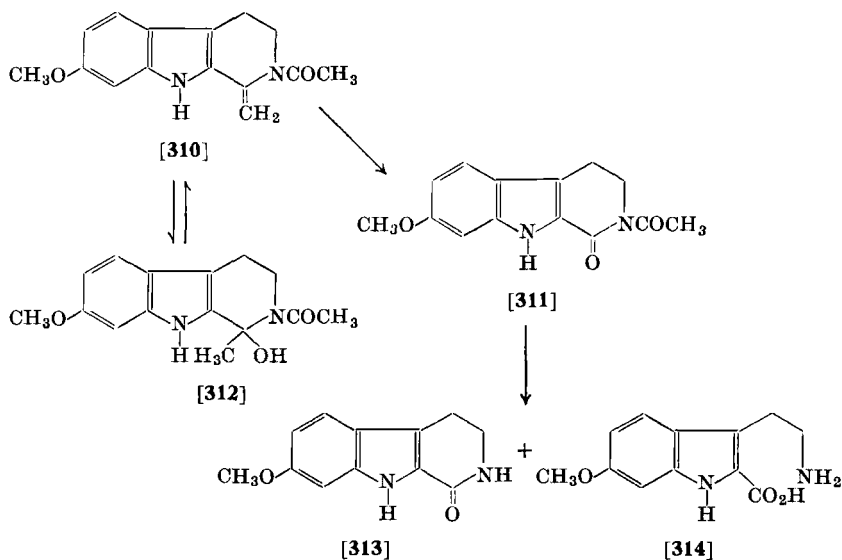
³⁵² J. Fritzsche, *Ann. Chem.* **72**, 306 (1849).

³⁵³ J. Gardent, *Bull. Soc. Chim. France* 1260 (1957).

³⁵⁴ R. N. Gupta and I. D. Spenser, *Can. J. Chem.* **40**, 2041 (1962).

alkylation of the anhydro-bases derived from these quaternary salts is accompanied by ring cleavage, yielding quaternary derivatives of 2-acetyltryptamine (see Section VI).

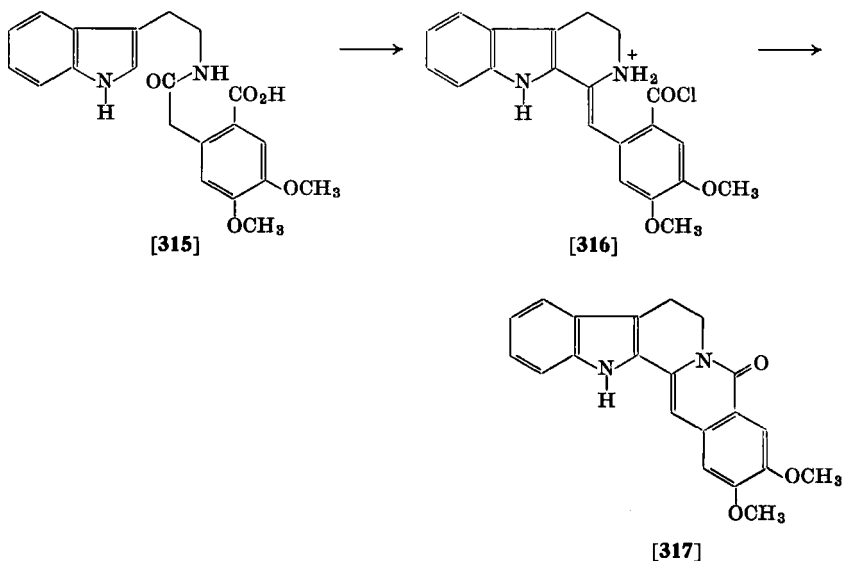
pyr-N-Acetylation of a 3,4-dihydro- β -carboline derivative has been reported. O. Fischer¹⁴⁶ described an *N*-acetylharmaline which was formulated as **310**¹⁵¹ since on controlled permanganate oxidation it yielded a neutral product (**311**), which on hydrolysis gave 7-methoxy-1-oxo-1,2,3,4-tetrahydro- β -carboline (**313**); the constitution of **313**



was later established by independent synthesis.^{173, 232} A second product obtained from the hydrolysis of the oxidation product (**311**), 6-methoxytryptamine-2-carboxylic acid (**314**), has also been synthesized.¹⁷³ Reduction of acetylharmaline gave a product which was identical with an authentic specimen of 2-acetyl-7-methoxy-1-methyl-1,2,3,4-tetrahydro- β -carboline.¹⁵¹ There is thus no reason to doubt the structure assigned to acetylharmaline; nevertheless, a reinvestigation of the chemistry of this compound would be desirable. In the 3,4-dihydroisoquinoline series analogous compounds appear to be unknown. A number of remarkable derivatives of acetylharmaline have been described, but their structures have not been clarified. Ethanolic hydrochloric acid converts acetylharmaline (**310**) into a

base, $C_{15}H_{18}O_3N_2$,^{151, 355} which is stable to permanganate, is reconverted into harmaline on treatment with alcoholic potassium hydroxide, and yields two different diacetyl derivatives on acylation.¹⁵¹ Structure **312** was favored for the base, but this clearly requires reinvestigation.

An analogous acylation reaction has been described in another 3,4-dihydro- β -carboline derivative. The amide **315**, on Bischler-Napieralski ring closure with phosphorus oxychloride, yields an



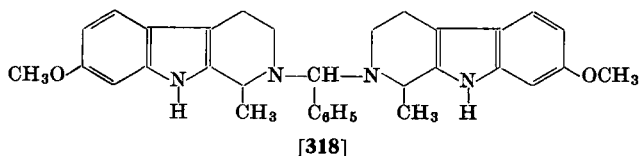
intermediate (**316**) which on the basis of its ultraviolet and infrared spectra was formulated as a 1-benzylidenetetrahydro- β -carboline derivative rather than as a 1-benzylidihydro compound. Treatment of this compound with base leads to intramolecular acylation at the *pyr-N* to yield a pentacyclic lactam whose structure was established by conversion into a compound of known constitution.⁷⁴ It was suggested that the Bischler-Napieralski cyclization of homophthalic acid derivatives of tryptamine (see Section III, C, 1, a) may proceed by way of intermediates analogous to **316**.

1,2,3,4-Tetrahydro- β -carboline derivatives can be monoalkylated

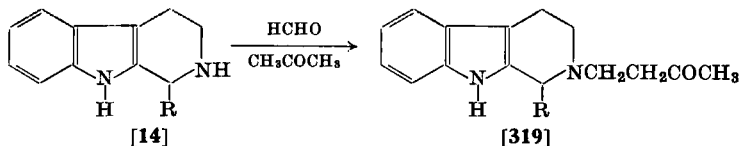
³⁵⁵ O. Fischer, *Prinzregent Luitpold Festschrift, Erlangen* 1901; *Chem. Zentr.* **72** (i), 959 (1901); *J. Chem. Soc.* **80**, 405 (1901).

at the *pyr-N* with alkyl halide.^{16, 71, 356, 357} Propylene oxide may also be used.^{357a} 1-Alkyl-1,2,3,4-tetrahydro- β -carboline-3-carboxylic acids resisted *N*-alkylation,³⁸ presumably due to steric crowding, but possibly due to lack of pH control.

The Eschweiler reaction (formaldehyde and formic acid) has been used for the *pyr-N*-methylation of 1-methyl-1,2,3,4-tetrahydro- β -carboline,²¹ as has formaldehyde and hydrogen in the presence of Raney nickel.¹⁴ Tetrahydroharmine has been reported to react with benzaldehyde to yield a condensation product, $C_{33}H_{36}N_4O_3$,¹⁴⁷ which is presumably a *pyr-N*-substituted derivative (**318**).⁷² It is not known whether a similar condensation product of benzaldehyde with harmaline^{147, 335} is a *C*- or *N*-substituted derivative of harmaline. Condensation at the 1-methyl group has been postulated,²¹⁰ but not proved.



The Mannich reaction has been employed to obtain the *pyr-N*-substituted 1,2,3,4-tetrahydro- β -carboline **319**,³⁵⁸ and intramolecular Mannich reactions at the *pyr-N* of suitably 1-substituted 1,2,3,4-tetrahydro- β -carboline with formaldehyde^{29, 68, 75-77, 149, 359-361} and



other aldehydes⁷² have been used to extend the carboline ring system (cf. Section V). An attempt to use this approach in the ring closure of the tetrahydrocarboline **320** to yield **321** was unsuccessful.²⁷ Addition

³⁵⁶ M. Protiva, Z. J. Vejdšek, J. O. Jílek, and K. Macek, *Collection Czech. Chem. Commun.* **24**, 3978 (1959).

³⁵⁷ A. L. Mndzhoyan, A. A. Aroyan, and S. G. Agbalyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **13**, 211 (1960); *Chem. Abstr.* **55**, 12438 (1961).

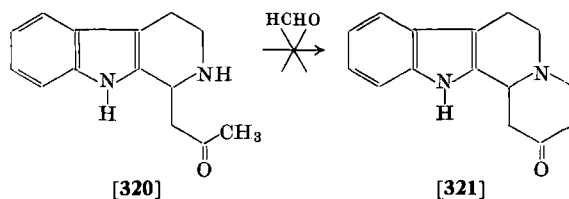
^{357a} A. M. Ahsan and W. H. Linnell, *J. Chem. Soc.* 3928 (1963).

³⁵⁸ K. B. Prasad and G. A. Swan, *J. Chem. Soc.* 2045 (1958).

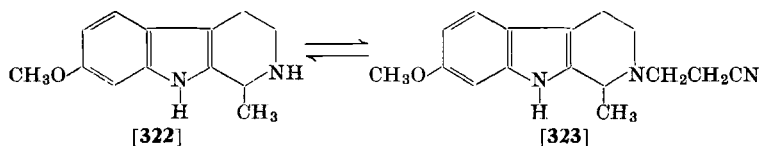
³⁵⁹ G. Hahn and A. Hansel, *Ber.* **71**, 2192 (1938).

³⁶⁰ T. Nogradi, *Monatsh. Chem.* **88**, 1087 (1957).

³⁶¹ J. H. Short, M. Freifelder, and G. R. Stone, *J. Org. Chem.* **26**, 2560 (1961).



of acrylonitrile or ethyl acrylate also leads to *pyr-N*-substituted products.^{27, 78, 362} The 2-cyanoethyl derivative (**323**) of 7-methoxy-1-methyl-1,2,3,4-tetrahydro- β -carboline (**322**) undergoes a base-catalyzed reversal of Michael addition.³²²



Tertiary *pyr-N*-alkyl-1,2,3,4-tetrahydro- β - and - γ -carboline derivatives can be quaternized at the same site to give 2,2-dialkyl-1,2,3,4-tetrahydro- β -^{14, 16, 22, 23, 55, 147, 150, 314, 357} and - γ -carbolinium^{14, 21} salts. Tertiary tetrahydro- β -carboline derivatives have been reported to yield *pyr-N*-oxides.^{218, 363}

Alkylation at the *ind-N* of 1,2,3,4-tetrahydro- β -carbolines has been carried out with alkyl halide after treatment with sodamide²¹ in the usual manner. Cyanoethylation of a *pyr-N*-substituted tetrahydro- β -carboline in the presence of Triton B yields the corresponding β -cyanoethyl derivative.³⁶² Similarly, treatment of *pyr-N*-methyl-1,2,3,4,4a,9b-hexahydro- γ -carboline with sodamide, followed by benzyl chloride, leads to the *ind-N*-benzyl-substituted derivatives.¹⁸⁰ 1-Oxo-1,2,3,4-tetrahydro- β -carboline yields the *ind-N*-methyl derivative directly with dimethyl sulfate.¹⁷³ Prolonged treatment with sodium hydride, followed by methyl iodide, yields the 2,9-dimethyl derivative.¹⁷³ Heating with sodium hydride in acetone followed by the addition of dimethyl sulfate gives rise to the *ind-N*-methyl derivative.^{363a}

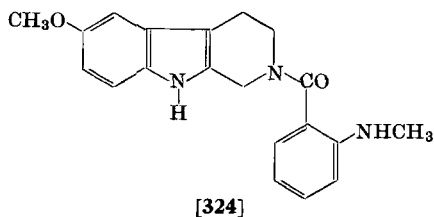
Acylation of 1,2,3,4-tetrahydro- β -carboline derivatives takes place preferentially at the *pyr-N*. Thus 1,2,3,4-tetrahydro- β -carboline yields a 2-formyl and a 2-acetyl derivative, which give 2-methyl-³⁶⁴

³⁶² S. G. Agbalyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **14**, 611 (1961).

³⁶³ P. R. Ulshafer, W. I. Taylor, and R. H. Nugent, *Compt. Rend.* **244**, 2989 (1957).

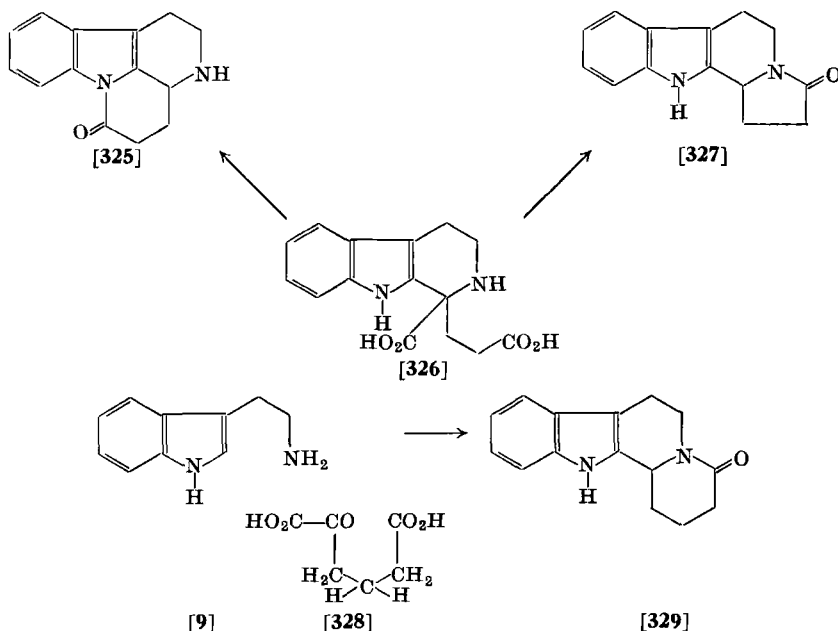
^{363a} F. D'Alo and A. Masserini, *Ann. Chim. (Rome)* **53**, 224 (1963); *Chem. Abstr.* **59**, 8715 (1963).

³⁶⁴ B. Witkop and S. Goodwin, *J. Am. Chem. Soc.* **75**, 3371 (1953).



and 2-ethyl-1,2,3,4-tetrahydro- β -carboline,⁷¹ respectively, on reduction with lithium aluminum hydride. The 2-acetyl⁷¹ and benzoyl³⁶⁵ (presumably 2-benzoyl) derivatives of 1-methyl-1,2,3,4-tetrahydro- β -carboline have also been described. Reaction of 6-methoxy-1,2,3,4-tetrahydro- β -carboline with *N*-methylisatoic anhydride gave the *pyr-N*-aroyl derivative **324**.¹⁷⁵ Both nitrogens of a tetrahydrocarboline can be acylated, 1,2,3,4-tetrahydro- β -carboline yielding the 2,9-diacetyl derivative.³⁶⁶

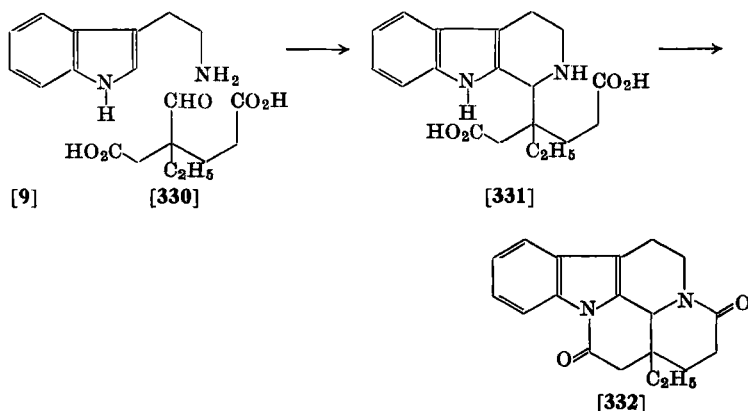
Intramolecular acylation of suitably 1-substituted 1,2,3,4-tetrahydro- β -carboline has been studied. It has been stated²⁹⁶ that



³⁶⁵ G. M. Badger and A. F. Beecham, *Nature* **168**, 517 (1951).

³⁶⁶ E. E. van Tamelen, K. V. Siebrasse, and J. B. Hester, *Chem. Ind. (London)* 1145 (1956).

whenever a choice exists between acid-catalyzed lactam formation onto either the *ind-N* or the *pyr-N* of a tetrahydro- β -carboline, the preference is always wholly toward the δ -lactam. The tetrahydro-carboline derivative **326**, obtained by reaction of tryptamine with α -ketoglutaric acid, gave the basic *ind-N*- δ -lactam **325** on treatment with ethanolic hydrogen chloride,^{69, 70} whereas condensation of tryptamine with α -ketoadipic acid (**328**) in acetic acid solution gave the non-basic *pyr-N*- δ -lactam **329**.⁷⁰ Similarly, the dilactam **332** was obtained on condensation of tryptamine with β -ethyl- β -formyladipic acid (**330**)

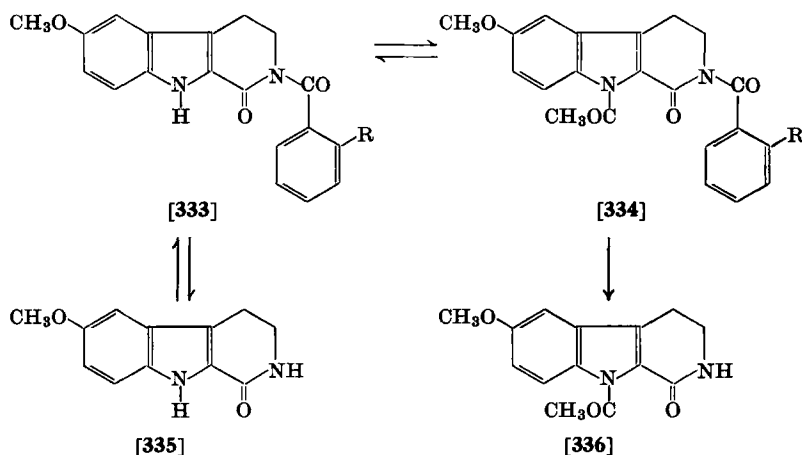


followed by treatment of the condensation product **331** with polyphosphoric acid.²⁹⁶ On the other hand it has been reported that condensation of tryptamine with α -ketoglutaric acid in acetic acid, or pyrolysis of the tetrahydrocarboline **326**, leads to the non-basic *pyr-N*- γ -lactam **327** rather than to the basic *ind-N*- δ -lactam **325**.⁷⁰ Acylation of *pyr-N*-methyl-1,2,3,4,4a,9b-hexahydro- γ -carboline (**93**) at the *ind-N* takes place readily. With acyl chlorides the corresponding 5-acyl derivative is obtained, and with phenylisocyanate or phenylthiocyanate the corresponding 5-phenylcarbamide and phenylthiocarbamide are formed.^{180, 367}

Acylation of 1-oxo-1,2,3,4-tetrahydro- β -carboline derivatives in the presence of phosphorus oxychloride takes place at the *pyr-N*. Thus 1-oxo-1,2,3,4-tetrahydro- β -carboline yields the 2-benzoyl derivative³⁵⁰ and 6-methoxy-1-oxo-1,2,3,4-tetrahydro- β -carboline (**335**) is

³⁶⁷ N. F. Kucheroва, I. G. Zhukova, N. N. Kamzolova, M. I. Petruchenko, N. M. Sharkova, and N. K. Kochetkov, *J. Gen. Chem. USSR (Eng. Transl.)* **31**, 858 (1961).

converted into the corresponding 2-acetyl¹⁷⁶ and 2-benzoyl (**333**; R = H)³⁴⁹ derivatives on treatment with acetic anhydride and benzoyl chloride, respectively. A 2-aryl-1-oxo-1,2,3,4-tetrahydro- β -carboline (**333**) can be further acetylated at the *ind-N* to yield the *ind-N*-acetyl-*pyr-N*-aryl derivative (**334**), which on mild hydrolysis in methanol loses the *pyr-N*-aryl group to yield the *ind-N*-acetyl-1-oxo-1,2,3,4-tetrahydro compound (**336**). Acid hydrolysis, on the other hand, leads to hydrolysis at the *ind-N*.¹⁷⁵ *pyr-N*-Acetylation of 1-oxo-1,2,3,4-tetrahydro- β -carboline takes place readily in the absence of phosphorus oxychloride.¹⁷⁸



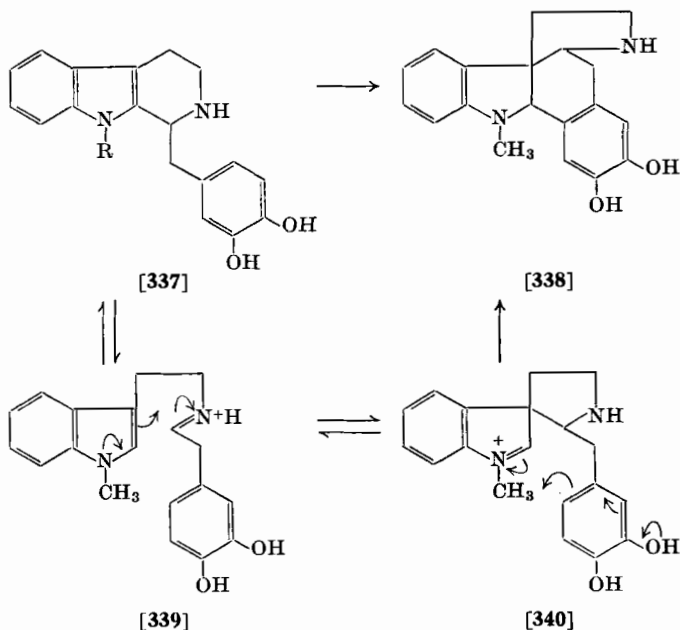
3. Reduction, Oxidation, Ring Opening, and Rearrangements

The oxidative and reductive interconversions of different oxidation states of the carboline ring system are systematically discussed in Section III.

A number of intramolecular rearrangements of 1,2,3,4-tetrahydro- β -carboline derivatives have been reported. Some of these lead into other naturally occurring heterocyclic ring systems and are therefore of particular interest.

The acid-catalyzed conversion of the 1,2,3,4-tetrahydro- β -carboline derivative **337** (R = CH₃) into the "strychnine-type" ring system **338** has been attributed³⁶ to an equilibrium involving the protonated Schiff's base **339** of tryptamine (i.e., the intermediate in the Pictet-Spengler type synthesis of tetrahydro- β -carboline, cf. Section III, A, 1, a), and the α - (**337**) and the β -condensation products (**340**).

The latter, which is not normally isolated, may, under favorable conditions, be trapped in the presence of a strong nucleophile, as in the conversion of **340** into **338**. It was surmised that the biogenetically modelled synthesis of strychnine-type systems³⁷ was a demonstration of such a reaction.

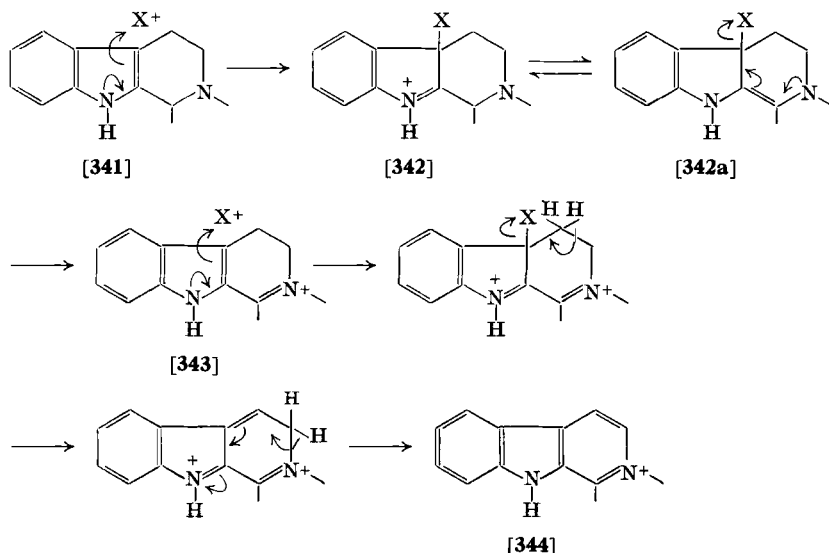


A series of oxidative rearrangements of tetrahydro- β -carboline may be rationalized on the basis of a general reaction of 2,3-disubstituted indoles which was recently recognized by Taylor.³⁶⁸ Attack at the 4a-position of the tetrahydrocarboline (**341**) by an electrophile yields the indolenine derivative **342**, which is in equilibrium with the isomeric species **342a**. Compounds of structure **342** and **342a** can undergo a variety of reactions leading to different products.

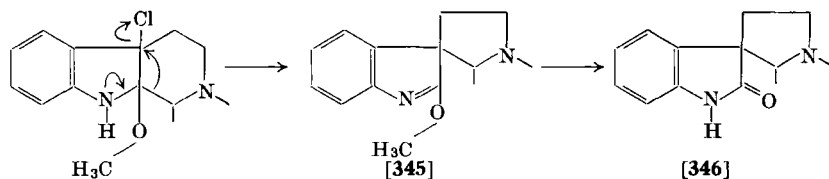
The oxidation of tetrahydro- β -carboline to dihydro- β -carbolinium salts (**341** \rightarrow **342** \rightleftharpoons **342a** \rightarrow **343**) by *t*-butyl hypochlorite ($X = \text{Cl}$), dichromate, or mercuric acetate (cf. Section III, C, 2, b), followed by treatment with acid, and to β -carbolinium salts (**341** \rightarrow **344**) by lead tetraacetate [$X = \text{Pb}(\text{OAc})_3$] (cf. Section III, E, 2, a, ii) in acid solution

³⁶⁸ W. I. Taylor, *Proc. Chem. Soc.* 247 (1962).

are special cases of this reaction. If the mixture of epimeric chloroindolenines (**342**; X = Cl), which can be isolated from the products of the reaction with *t*-butyl hypochlorite, is treated with methanol in the



presence of base, rearrangement to the imido ether **345** takes place; on mild acid hydrolysis **345** yields a mixture of the epimeric 3,3-spirooxindoles (**346**).^{218, 369, 370} The 3,3-spirooxindole ring system is found

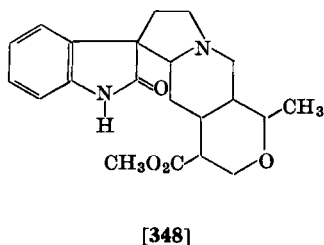
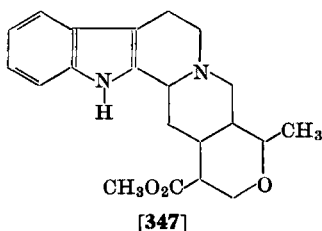


in a number of alkaloids, and a general method for the conversion of tetrahydro- β -carboline alkaloids [e.g. ajmalicine (**347**)] into the corresponding oxindole alkaloids [e.g. mitraphylline (**348**)] by way of the corresponding chloroindolenines is thus available. A similar conversion of a simple tetrahydro- β -carboline (**349**) in which the nitrogen atoms

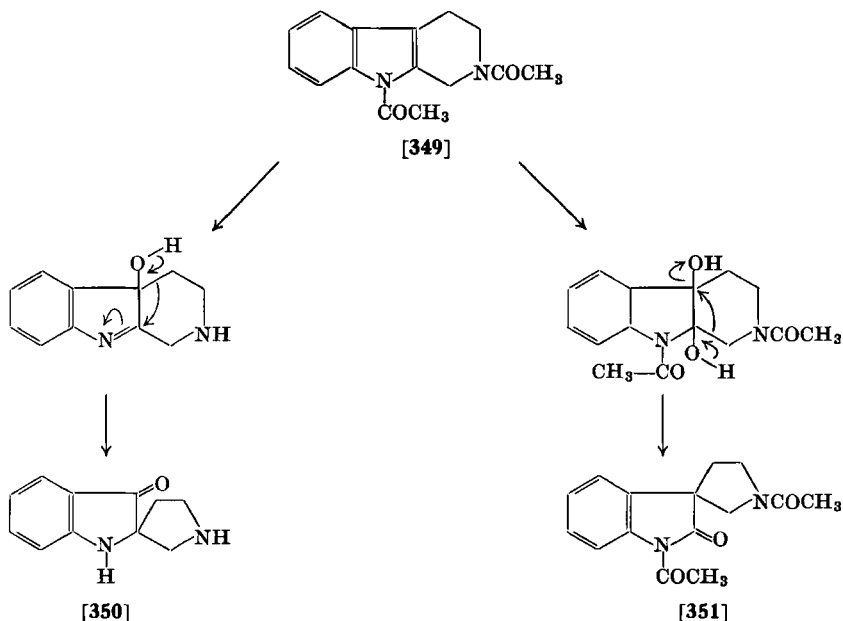
³⁶⁹ N. Finch and W. I. Taylor, *J. Am. Chem. Soc.* **84**, 1318 (1962).

³⁷⁰ J. Shavel, Jr., and H. Zinnes, *J. Am. Chem. Soc.* **84**, 1320 (1962).

were protected by acylation has been brought about with osmium tetroxide³⁶⁶ to yield the 3,3-spirooxindole **351** under conditions which avoid hydrolysis of the *N*-acyl groups. The reaction has been likened

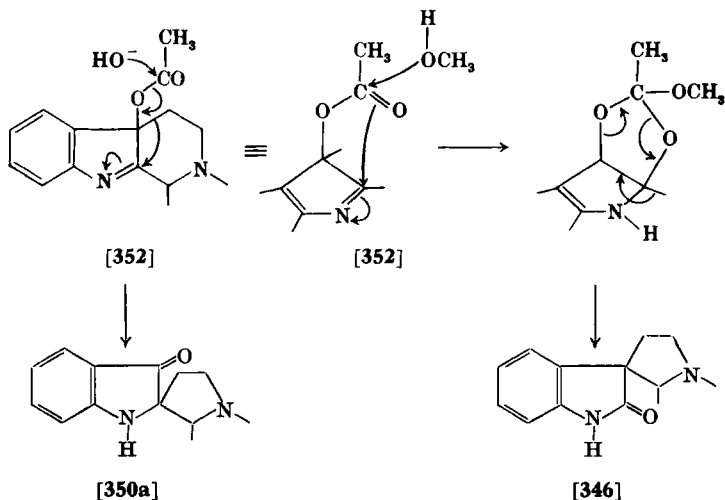


to a pinacol-pinacolone rearrangement. A different rearrangement takes place under basic conditions which permit hydrolysis of the *N*-acyl groups. A benzilic-type rearrangement yielding the 2,2-spiropseudoindoxyl derivative **350**³⁶⁶ occurs, analogous to the conversion of ibogaine into iboluteine.³⁷¹ Similar rearrangements can be achieved



³⁷¹ R. Goutarel, M.-M. Janot, F. Mathys, and V. Prelog, *Helv. Chim. Acta* **39**, 742 (1956).

with lead tetraacetate at room temperature. In the absence of acid, **341** ($X = \text{AcO}$) yields two epimeric indolenine acetates (cf. **352**) both of which undergo the base-catalyzed rearrangement to pseudoindoxyl derivatives (**350a**). In the presence of dilute acid only the epimer bearing an acetyl group axial with respect to ring C rearranges to



an oxindole derivative (**346**). The indolenine acetate with an equatorial acetyl group is stable under these conditions.³⁷² Related rearrangements had been investigated earlier in the tetrahydrocarbazole series³⁷³ and have been studied in other indole systems.²¹⁶

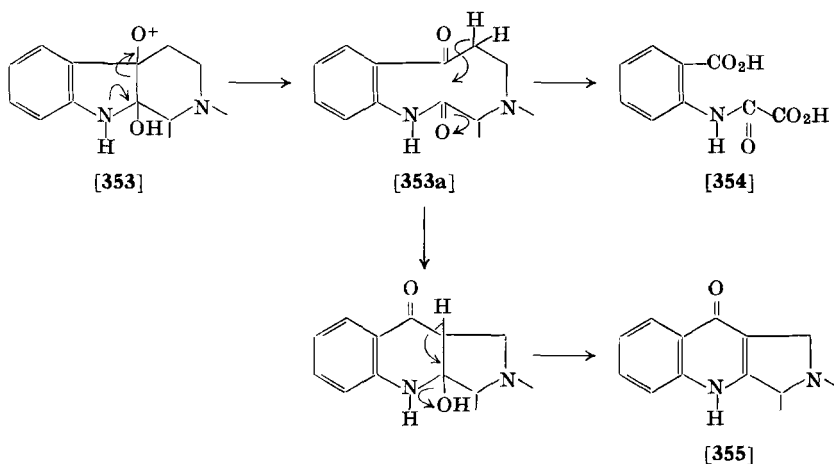
The same general intermediate (**342**; $X = \text{OOH}$) may be invoked⁶ in the reaction of tetrahydro- β -carboline derivatives with perbenzoic acid²⁹⁵ and ozone.³⁶⁴ From the reaction [**342** ($X = \text{OOH}$) \rightarrow **353** \rightarrow **353a**] a cyclic lactam (**353a**) may be isolated. Such a structure is presumably the intermediate in the oxidative degradation of numerous complex tetrahydro- β -carboline alkaloids, which yields *N*-oxalyl-anthranilic acid derivatives (**354**).^{340, 374} The lactam can undergo base-catalyzed cyclization to a pyrroloquinolone derivative (**355**).^{282, 364}

³⁷² W. I. Taylor, private communication (1962).

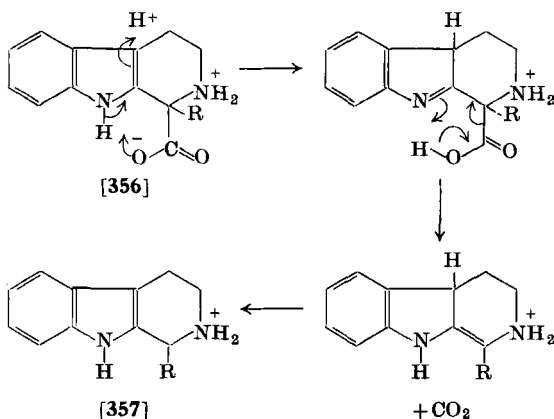
³⁷³ B. Witkop, *J. Am. Chem. Soc.* **72**, 614 (1950); J. B. Patrick and B. Witkop, *J. Am. Chem. Soc.* **72**, 633 (1950); B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 2188, 2196 (1951).

³⁷⁴ E. Späth and H. Bretschneider, *Ber.* **63**, 2997 (1930).

The alkaloid iboquine, a piperidinoquinoline, was derived in an analogous manner by air-oxidation of ibogaine, an indole derivative.³⁷⁵

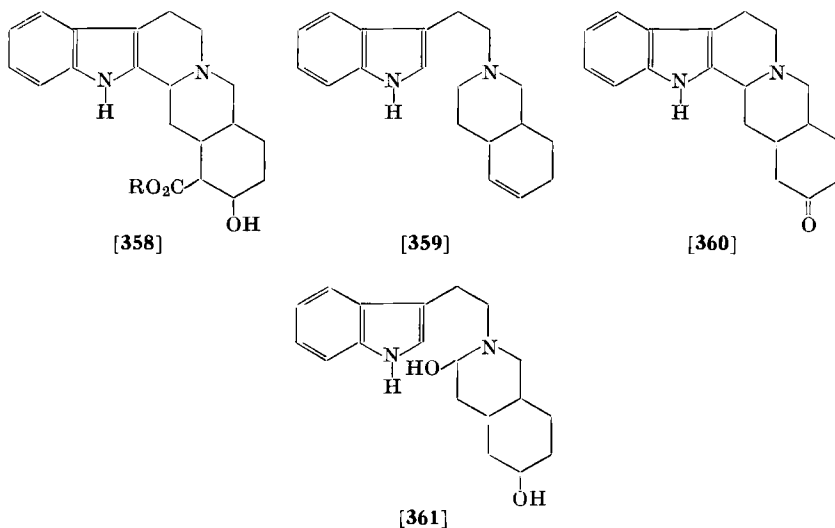


Implication of the same type of intermediate (**342**; X = H) allows the rationalization of the acid-catalyzed decarboxylation of 1,2,3,4-tetrahydro- β -carboline-1-carboxylic acids. As is stated in Section III, A, 1, a, the tetrahydroisoquinoline-1-carboxylic acids and α -amino acids of analogous structure are converted into the corresponding

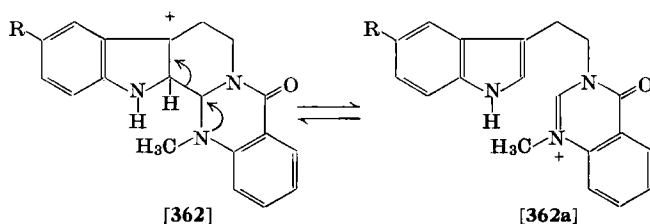


³⁷⁵ R. Goutarel and M.-M. Janot, *Ann. Pharm. Franç.* **11**, 272 (1953); *Chem. Abstr.* **47**, 8969 (1953).

esters and do not suffer decarboxylation under conditions leading to the conversion of tetrahydrocarboline-1-carboxylic acids into the corresponding tetrahydro- β -carbolines. The reaction is clearly a function of the indole structure. The mechanism outlined (**356** \rightarrow **357**) provides a satisfactory explanation for the decarboxylation reaction.



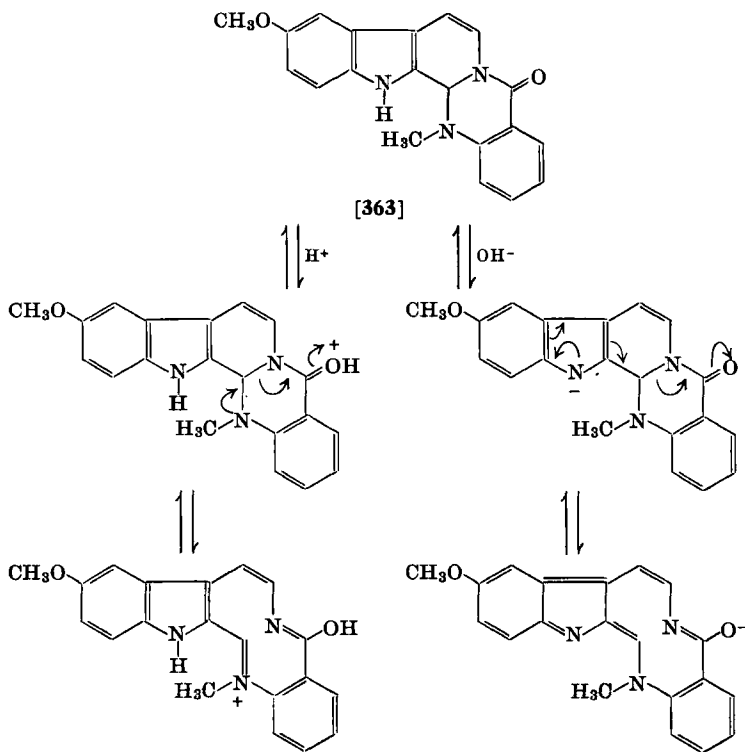
A different mode of ring cleavage was encountered when yohimbic acid (**358**; R = H) was treated with thallous oxide or carbonate.³⁷⁶ The tryptamine derivative **359** and yohimbone (**360**) were isolated in small yield. It was suggested that the primary cleavage product (**361**) undergoes an intermolecular oxidation-reduction reaction with yohimbic acid (**358**; R = H) to give **359** and a β -keto acid which decarboxylates to yohimbone (**360**). Cleavage at the same site is believed to be



³⁷⁶ B. Witkop, *J. Am. Chem. Soc.* **71**, 2259 (1949).

involved in the conversion, in dilute alcoholic hydrochloric acid, of evodiamine (**113**; $R = H$)^{202, 291, 377} and dihydrohortiamine (**113**; $R = OCH_3$)³⁴⁹ into isoevodiamine and its 5-methoxy derivative (**362a**), respectively (cf. $113 \rightleftharpoons 362a \rightleftharpoons 362$).

Treatment of isohortiamine (**363**) with acid or base leads to a pronounced change in the visible and ultraviolet absorption spectra. The structures shown, in which the 1,2-bond of the β -carboline moiety

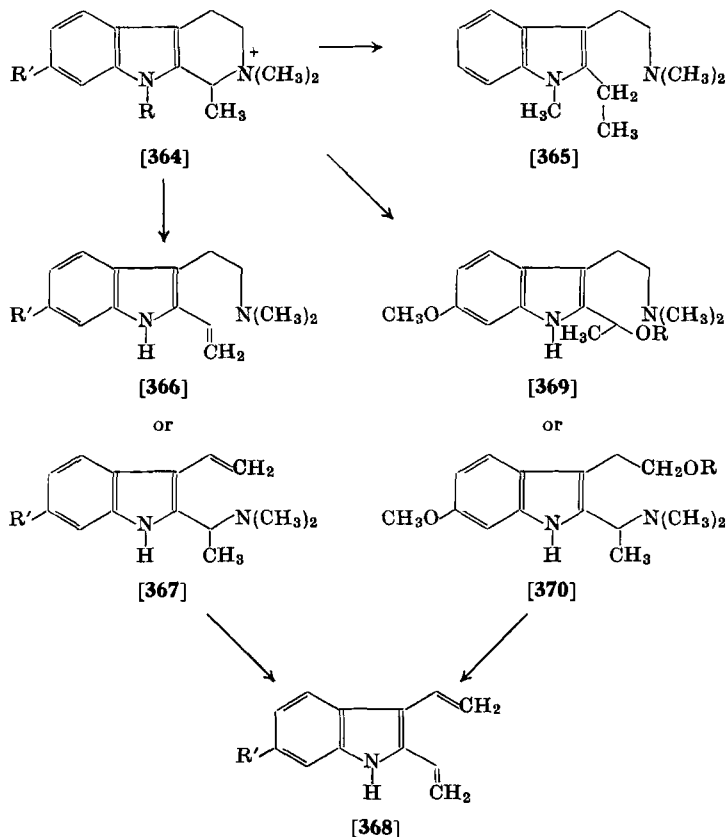


has cleaved, have been assigned to the intensely yellow species produced under these conditions.¹⁷⁵ These assignments require confirmation, but a possible mechanism is shown. It is noteworthy that earlier attempts at oxidative or reductive cleavage of the 1,2-bond of a complex tetrahydro- β -carboline had failed.³⁶⁴

The Hofmann and Emde degradation of tetrahydro- β -carboline derivatives has been reported in a number of instances, but only in one

³⁷⁷ T. Ohta, *J. Pharm. Soc. Japan* **65**, 15 (1945); *Chem. Abstr.* **45**, 5697 (1951).

study has the product been clearly identified. Emde degradation of 1,2,2,9-tetramethyl-1,2,3,4-tetrahydro- β -carbolinium iodide (**364**; $R = CH_3$, $R' = H$) gave N_{β} -dimethyl-2-ethyl-1-methyltryptamine (**365**).³⁷⁸ The structure of the Hofmann-degradation product of 1,2,2-trimethyl-1,2,3,4-tetrahydro- β -carboline (**364**; $R = R' = H$) has

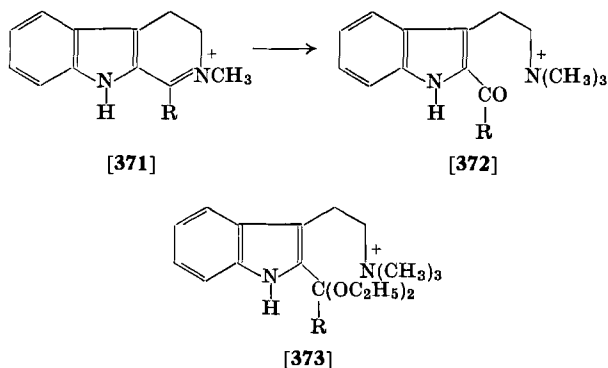


not been established. This product (**366** or **367**; $R' = H$) yielded a methiodide which, on further treatment with base, gave an intractable glassy solid, presumably a polymer of 2,3-divinylindole (**368**; $R = H$).²³ Exhaustive methylation of 2-methyl-1,2,3,4-tetrahydro- β -carboline has also been reported, but proof of structure of the intermediates and

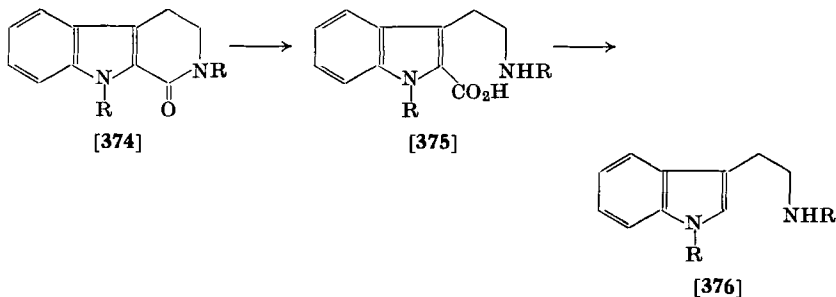
³⁷⁸ E. Leete, *J. Am. Chem. Soc.* **82**, 6338 (1960).

the end-product was not offered.⁵⁵ Exhaustive methylation of 7-methoxy-1,2,2-trimethyl-1,2,3,4-tetrahydro- β -carbolinium iodide (**364**; $R = H$, $R' = OCH_3$) leads to a similar polymeric material (presumably **368**; $R' = OCH_3$),¹⁵⁰ but the intermediate appears to be the corresponding displacement product (**369** or **370**),^{147, 150} not the elimination product (**366** or **367**; $R' = OCH_3$).

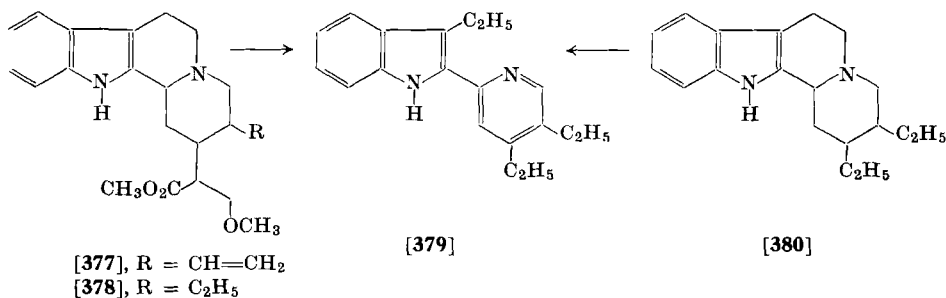
Alkylation of 3,4-dihydro- β -carboline methiodide (**371**; $R = H$)¹⁹² and of 1-methyl-3,4-dihydro- β -carboline methiodide (**371**; $R = CH_3$)³⁵⁴ in alkaline solution is accompanied by ring cleavage, and gives quaternary 3-acyltryptamine derivatives (**372**) or their acetals (**373**) depending on reaction conditions.



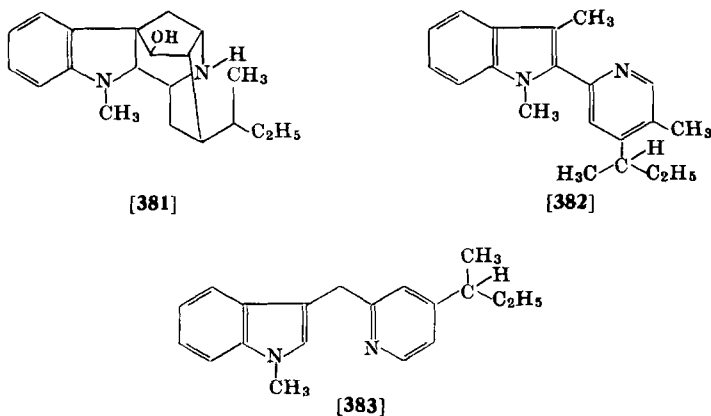
Ring cleavage of 1-oxo-1,2,3,4-tetrahydro- β -carboline derivatives (**374**) may be accomplished by base-catalyzed hydrolysis to yield tryptamine-2-carboxylic acids (**375**).^{172, 173, 234} In the case of the 1,9-dimethyl derivative decarboxylation accompanied acid-catalyzed ring-opening, and the corresponding tryptamine (**376**) was obtained directly.¹⁷³



Cleavage of the hetero ring in a number of extended tetrahydro- β -carboline systems was observed in the course of structural elucidation of tetrahydro- β -carboline alkaloids. A few examples only will be given. The indole derivative **287** was isolated as one of the products of the selenium dehydrogenation of yohimbine (**358**; $R = CH_3$)^{338, 379} and



was also obtained by pyrolysis of yohimbic acid (**358**; $R = H$).³³⁶ An analogous compound (**379**) was obtained by selenium dehydrogenation of corynantheine (**377**; $R = CH=CH_2$)³⁸⁰ and of corynantheidine (**378**; $R = C_2H_5$).³⁸¹ Compound **379** was also obtained from the tetrahydro- β -carboline **380** on distillation with palladium.^{381, 382}



³⁷⁹ F. Mendlik and J. P. Wibaut, *Rec. Trav. Chim.* **50**, 91 (1931).

³⁸⁰ P. Karrer and P. Enslin, *Helv. Chim. Acta* **32**, 1390 (1949).

³⁸¹ M.-M. Janot, R. Goutarel, and J. Chabasse-Massonneau, *Bull. Soc. Chim. France* 1033 (1953).

³⁸² M.-M. Janot and R. Goutarel, *Bull. Soc. Chim. France* 588 (1951).

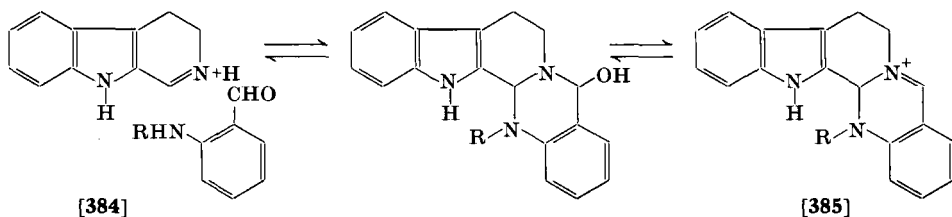
Palladium dehydrogenation of the hexahydro- β -carboline derivative dihydrodesoxyajmaline (**381**) yielded, among other degradation products which included fully aromatic β -carboline derivatives, the two substituted indoles **382** and **383**.^{383, 383a}

An instance of the pyrolytic ring cleavage of a quaternary 1,2-dihydro- γ -carbolinium salt to an indolenine derivative has been reported.⁸⁶

V. Ring Extension

It is not proposed to give here a comprehensive survey of the methods which have been used to add additional rings onto preformed carboline ring systems. Rather, a few examples only have been selected to illustrate the types of procedures involved. The interest in performing such ring extensions lies in the fact that many of them have been used to synthesize alkaloids containing the β -carboline ring system as well as degradation products, derivatives, and synthetic analogs of these alkaloids—the latter mainly in connection with studies on the relationship between structure and pharmacological activity (see, e.g., ref. 384).

The alkaloid rutaecarpine (**111**) was synthesized from 1-oxo-1,2,3,4-tetrahydro- β -carboline (**183**; R = H) by condensation with methyl anthranilate in the presence of phosphorous chloride³⁸⁵ or by heating with isatoic anhydride at 195°. ³⁸⁶ The alkaloid was also obtained by boiling 1-methoxy-3,4-dihydro- β -carboline (**152**; R = H, R' = CH₃) with anthranilic acid in methanol.³⁴⁸ In this connection might be



³⁸³ R. B. Woodward, *Angew. Chem.* **68**, 13 (1956).

^{383a} K. A. Schenker and R. B. Woodward, quoted by J. E. Saxton in "The Alkaloids" (R. H. F. Manske, ed.) Vol. 7, p. 109. Academic Press, New York, 1960.

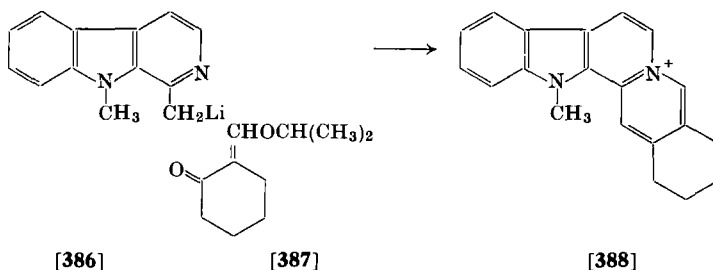
³⁸⁴ S. G. Agbalyan, *Uspekhi Khim.* **30**, 1175 (1961); *Chem. Abstr.* **56**, 3523 (1962).

³⁸⁵ Y. Asahina, R. H. F. Manske, and R. Robinson, *J. Chem. Soc.* 1708 (1927).

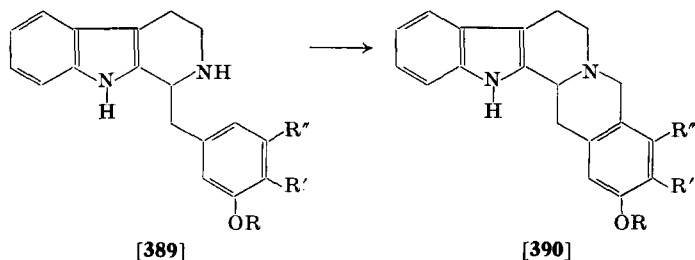
³⁸⁶ T. Ohta, *J. Pharm. Soc. Formosa* **51** (no p. given) (1938); *Chem. Abstr.* **34**, 5846 (1940); *J. Pharm. Soc. Japan* **60**, 311 (1940); *Chem. Abstr.* **34**, 7291 (1940).

mentioned the interesting work of Schöpf and Steuer¹⁹¹ on the biogenesis of rutaecarpine and evodiamine. Condensation of 3,4-dihydro- β -carboline (384) perchlorate with *o*-aminobenzaldehyde or *N*-methyl-*o*-aminobenzaldehyde at 25° and pH 5.0 gave the orange-colored pentacyclic compounds 385 (R = H) and 385 (R = CH₃), respectively, which were readily convertible into rutaecarpine (111) and evodiamine (113).

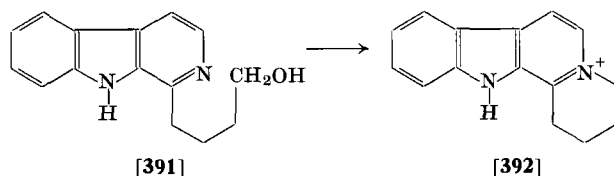
The synthesis of the 1-methyl derivative of sempervirine was achieved by Woodward and McLamore³³² who condensed 1-lithio-methyl-9-methyl- β -carboline (386) with 2-isopropoxymethylenecyclohexanone (387); treatment of the reaction product with hydrochloric acid gave *ind-N*-methylsempervirinium chloride (cf. 388).



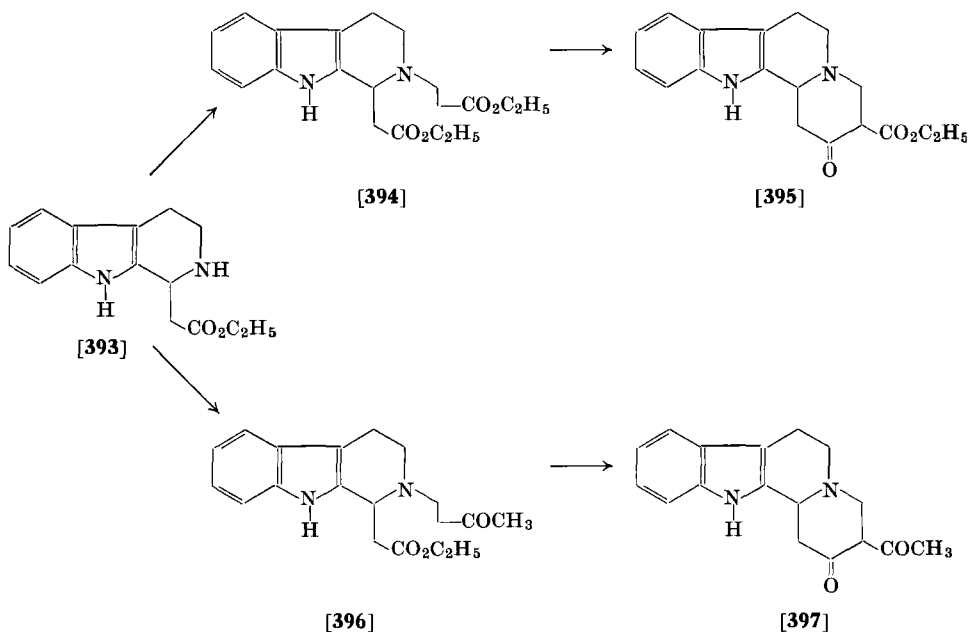
Compounds containing the yohimbine ring skeleton (390) have been synthesized by Hahn and his co-workers^{28, 68, 359} via an intramolecular Mannich reaction, and this method has recently been extended and repeatedly applied (see Section IV, B, 2). It involves treating a 1-*m*-hydroxybenzyl-1,2,3,4-tetrahydro- β -carboline derivative (389) with formaldehyde at pH 4.4. When the aqueous solution of the hydrochloride of the hydroxymethyl derivative so formed is made basic with sodium carbonate, the pentacyclic base (390) precipitates.



A number of successful approaches to the indolo[2,3-*a*]quinolizinium ring system (**252**) (generally leading to reduced derivatives) have been reported by Swan and co-workers. By treating 1-(4'-hydroxybutyl)-1,2,3,4-tetrahydro- β -carboline (**391**) with hydrobromic acid followed by base, 1,2,3,4-tetrahydro-12*H*-indolo[2,3-*a*]quinolizinium bromide

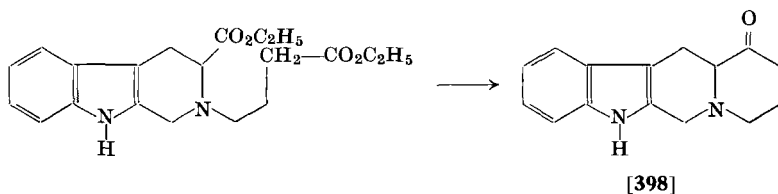


(**392**) was obtained.²⁷ An alternative route to this ring system was also developed.^{27, 386a} 1-Carbethoxymethyl-1,2,3,4-tetrahydro- β -carboline (**393**) was added to ethyl acrylate and the dicarboxylic ester **394** subjected to a Dieckmann cyclization, when the β -keto ester **395** was obtained in 15% yield, together with the isomeric keto ester resulting from the alternative mode of cyclization.^{78, 358}

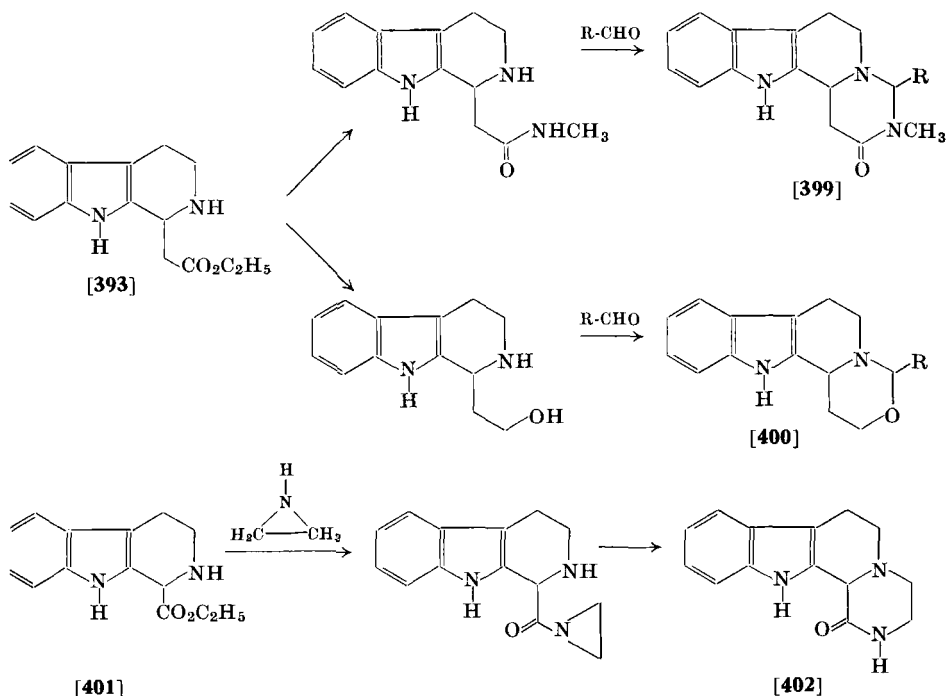


In a modified approach, the carbolinyl acetate **393** underwent a Mannich reaction with formaldehyde and acetone to give the keto ester **396** which, with base, cyclized to the diketone **397**.³⁵⁸ This diketone (**397**) has recently been used to prepare a number of interesting pentacyclic compounds.⁷²

A further application of the Dieckmann cyclization is that leading to the synthesis of 3,4,6,12-tetrahydro-1(2*H*)-indolo[2,3-*b*]quinolizin-1-one (**398**).⁹⁵



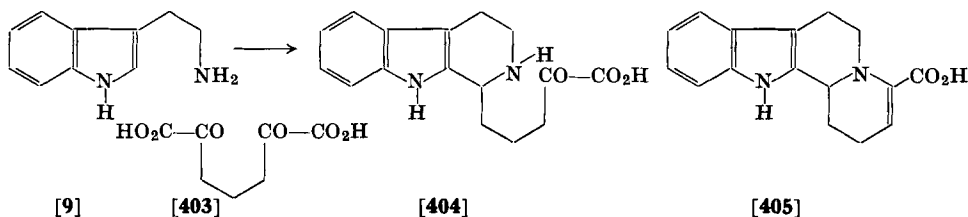
Starting from **393**, de Stevens and co-workers^{72, 386b} synthesized some new tetracyclic derivatives (**399** and **400**) using conventional



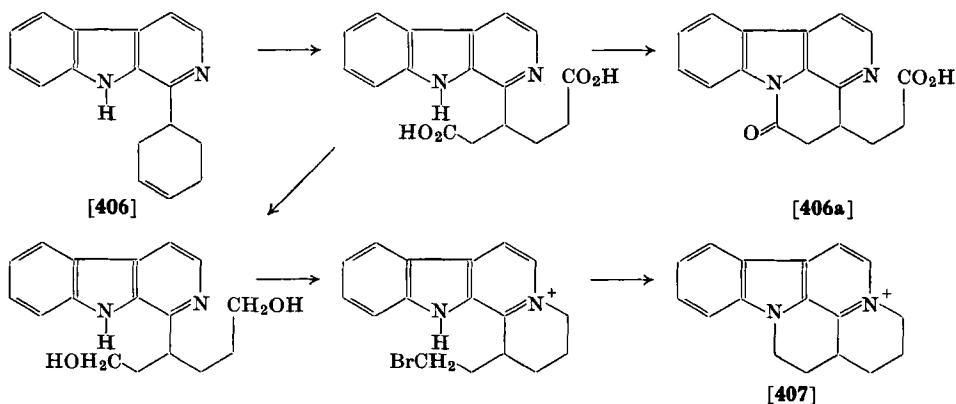
^{386b} G. de Stevens and M. Sklar, *J. Org. Chem.* **28**, 3210 (1963).

reactions. An unconventional route was used to convert ethyl tetrahydro- β -carboline-1-carboxylate (**401**) into the tetracyclic system **402**.³⁸⁷

The interesting work of Hahn and Hansel,⁶⁹ who prepared a tetracyclic lactam by intramolecular cyclization of the condensation product of tryptamine and α -ketoglutaric acid, is referred to in Section IV, B, 2. Condensation of tryptamine with α,α' -diketopimelic acid (**403**) led, presumably by way of the 1-substituted tetrahydro- β -carboline (**404**), which could not be isolated, to a product to which the tetracyclic structure **405** was assigned.



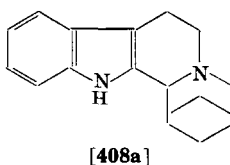
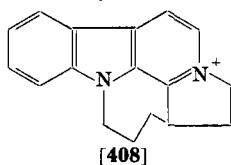
Mention must also be made of the neat series of reactions carried out by Wieland and Neeb⁷⁹ which led to a number of ring extended products. These are summarized by the conversion of **406** into **406a** and **407**. The structure of **406a** was confirmed by a comparison of its



ultraviolet absorption spectrum with that of dihydrocanthine. The postulated formation of two new six-membered rings leading to **407** was preferred by these authors over the alternative formulation (**408**)

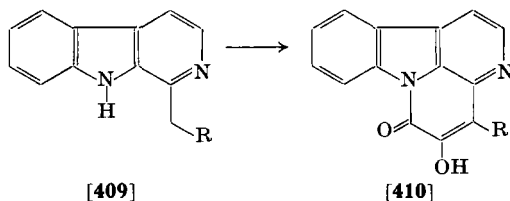
³⁸⁷ G. de Stevens, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)* **23**, 105 (1962).

for the final product, and this was supported by the subsequent work of Bartlett and Taylor.²⁹⁶

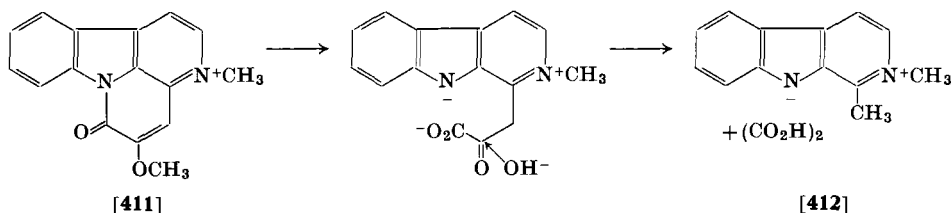


Intramolecular amide formation has also been used recently to obtain new pentacyclic ring systems, e.g. **408a**.^{387a, 387b}

Derivatives (**410**) of a canthinone may be prepared readily from the dilithio derivative of the appropriate β -carboline (**409**) by reaction with diethyl oxalate.²⁹⁶ Reversal of this condensation accounts for



the formation of a yellow base, $C_{13}H_{14}ON_2$, melting at $190-193^\circ$ (decomp.), on treatment of 5-methoxycanthin-6-one methiodide (**411**) with 10% alkali.³⁴² The product, which was formulated as a pseudo-base, is presumably the hydrate of 1,2-dimethyl- β -carboline anhydro-base **412** [reported melting points: $177-178^\circ$ (decomp.)⁴⁵, and about



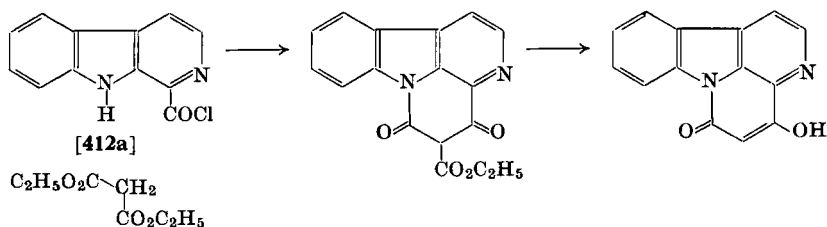
180° (decomp.), but variable, depending on method of purification and degree of hydration⁴³] generated from the canthinone derivative in the manner shown.

The canthinone ring system was also obtained by condensation of β -carboline-1-carbonyl chloride (**412a**) with diethyl malonate, followed

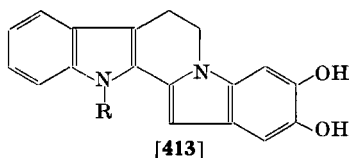
^{387a} F. Walls and G. Perez, *Bol. Inst. Quim. Univ. Nal. Auton. Mex.* **14**, 32 (1962); *Chem. Abstr.* **59**, 2784 (1963).

^{387b} G. Berti, A. Bonsignori, and A. Da Settimo, *Ann. Chim. (Rome)* **52**, 1087 (1962); *Chem. Abstr.* **59**, 12773 (1963).

by acid hydrolysis³⁴³ and by intramolecular amide formation onto the *ind-N* of 2-(1- β -carbolinyl)-*cis*-acrylic acid.²⁷⁹



The benzindolopyrrocoline system (**413**) was obtained by oxidative cyclization of the 1-benzyl-1,2,3,4-tetrahydro- β -carboline derivative (**337**; R = H or CH₃) using either ferricyanide or silver oxide,³⁸⁸ a reaction analogous to that described by Robinson³⁸⁹ and by Schöpf³⁹⁰ in the isoquinoline series.

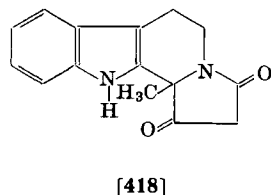
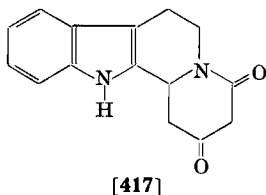
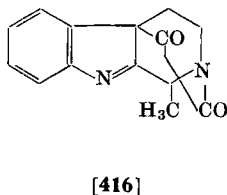
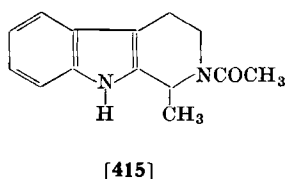
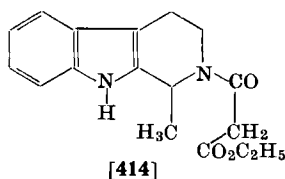


Finally, the remarkable reaction described by Tatsui^{16, 17} should be discussed. When 1-methyl-1,2,3,4-tetrahydro- β -carboline (tetrahydroharman) (**134**) was treated with diethyl malonate in the presence of sodium ethoxide a compound with the empirical formula C₁₇H₂₀N₂O₃, m.p. 134–135°, was isolated together with a small amount of a free acid. The latter liberated carbon dioxide on heating to give *pyr-N*-acetyltetrahydroharman (**415**). It would, therefore, seem likely that the C₁₇H₂₀N₂O₃ compound has the structure **414**. When this is treated with sodium ethoxide it gives a new compound, C₁₅H₁₄N₂O₂, formulated by Tatsui as the keto-amide **417**. It is difficult to see how such a structure could arise from **414** under the conditions of the reaction, and the nature of this product clearly needs re-investigation. A more probable structure would seem to be **418**, or possibly **416**, even though this would entail the formation of a seven-membered ring.

³⁸⁸ J. Harley-Mason and W. R. Waterfield, *Chem. Ind. (London)* 1478 (1960).

³⁸⁹ R. Robinson and S. Sugawara, *J. Chem. Soc.* 789 (1932).

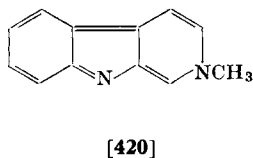
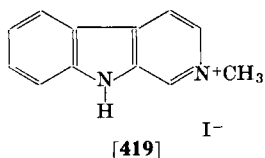
³⁹⁰ C. Schöpf and K. Thierfelder, *Ann. Chem.* **497**, 22 (1932).



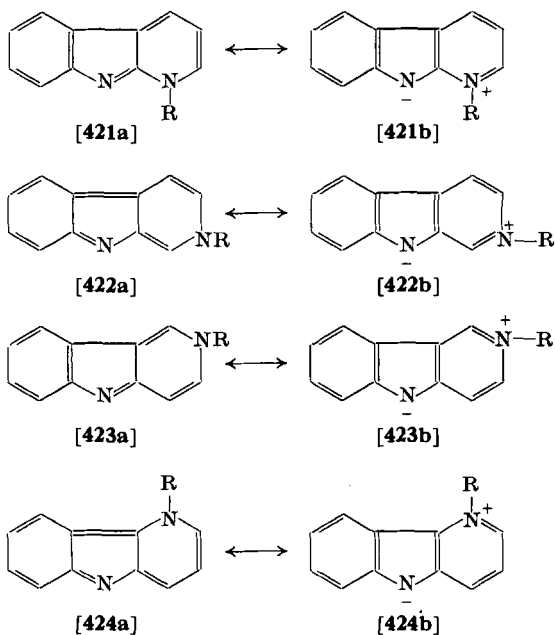
VI. Properties and Structure of the Anhydro-Bases

A. CARBOLINE ANHYDRO-BASES

When a *pyr-N*-alkylcarbolinium salt, unsubstituted at the *ind-N* atom, is treated with strong alkali, a yellow to deep orange, strongly basic solid separates. Although such products almost invariably give poor microanalytical values¹³⁰ they can be shown to be derived from the quaternary hydroxide by loss of a molecule of water—hence the name anhydro-bases or anhydronium bases.²⁶⁹ All four carbolines form anhydro-bases; e.g., *pyr-N*-methyl- β -carbolinium iodide (**419**) gives **420**. Most of the evidence bearing on the structures of these bases has been summarized,¹ and discussion will therefore be limited to a few of the recent aspects of the chemistry of these compounds.

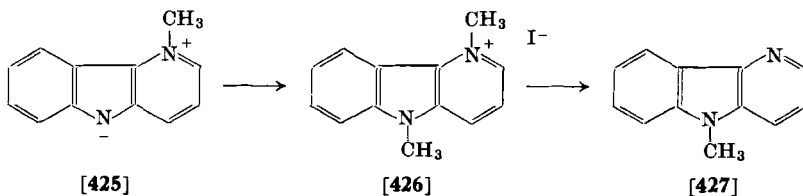


Armit and Robinson²⁶⁹ suggested that it was necessary to represent the structure of a carboline anhydro-base as a compromise between a quinonoid and a dipolar structure. In more current terminology, this means that they (cf. **421–424**) should be considered as resonance hybrids of structures **a** and **b** in which the tendency to attain the fully aromatic sextet of π -electrons is balanced by that to effect neutralization of the charges.



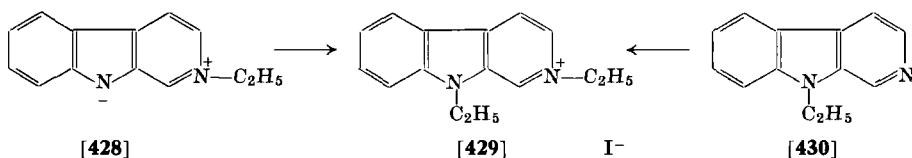
Support for this suggestion comes from many quarters. Reduction of the β -carboline anhydro-bases with sodium and alcohol or with tin and hydrochloric acid gives the 1,2,3,4-tetrahydro derivatives, as does catalytic reduction over platinum oxide in an alkaline medium. On the other hand, catalytic reduction with platinum oxide in acetic acid results in the formation of the 5,6,7,8-tetrahydro- β -carbolinium derivatives¹³⁰ (see Section III, A, 2, a). It should be noted, however, that reduction of pyrido[1,2-*b*]indazole, in which the dipolar structure **211** is the main contributor to the resonance hybrid, could not be effected with hydrogen in the presence of Adams' catalyst.²⁶²

Protonation and alkylation of the anhydro-bases (e.g. **425**) takes place at the *ind-N* atom (see Section IV, A, 2). The resulting *ind-N*-, *pyr-N*-dialkylcarbolinium salts (e.g. **426**) give the corresponding

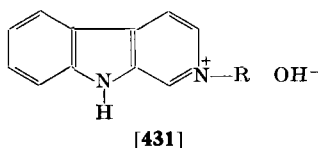


quaternary hydroxides on treatment with alkali, whereas, on dry distillation, the *pyr-N*-alkyl group is lost to give the *ind-N*-alkylated carbolines (e.g. **427**).^{45, 46, 263, 313}

That alkylation of the anhydro-bases takes place at the indole nitrogen atom in the β -carboline series was established conclusively by the identity of the product (**429**), prepared by treatment of *pyr-N*-ethyl- β -carboline anhydro-base (**428**) with ethyl iodide, with 2,9-diethyl- β -carbolinium iodide (**429**) obtained from the reaction of *ind-N*-ethyl- β -carboline (**430**) with ethyl iodide⁴¹ (see Section IV, A, 2).



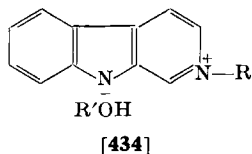
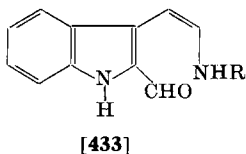
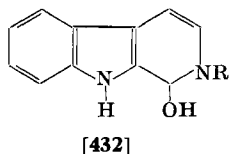
That the *ind-N* atom in the anhydro-bases is the basic center is also obvious from a consideration of the ultraviolet absorption spectra of the anhydro-bases. In aqueous 0.1*N* hydrochloric acid as well as in neutral alcoholic solutions each carboline anhydro-base gives rise to an ultraviolet absorption spectrum identical with that of the parent carbolinium salt. In alkaline solutions (pH above 11.5 in the case of the



β -carboline derivative) the absorption spectrum is that of the anhydro-base. Spenser³⁹¹ has made a careful study of the variation of the ultraviolet absorption spectrum of the β -carbolinium ion with pH. At pH values below 10.5, the curves obtained are identical with that given by the β -carbolinium ion. With increasing pH, at values between 10.5 and 11.5, the peaks due to the β -carbolinium ion at 255, 305, and 375 m μ gradually weaken in intensity and finally disappear, while the maxima due to the anhydro-base at 275 and 325 m μ appear as inflections and increase finally to their full intensities. This indicates an equilibrium between the quaternary hydroxide **431** and the anhydro-base **422** at pH values between 10.5 and 11.5. This interpretation is at

³⁹¹ I. D. Spenser, *J. Chem. Soc.* 3659 (1956).

variance with that of Schwarz and Schlittler¹³⁰ who, from a study of the spectra of the anhydro-bases in aqueous or alcoholic solution, concluded that in ionizing solvents the substances exist as pseudo-bases (**432**) in equilibrium with the aminoaldehyde (**433**) or as solvated molecules (**434**). On the basis of a comparison of the above spectra



with those of 3-formylindole, 2-formylindole, and 1,2-dihydro-2-methyl-1-oxo- β -carboline (which has a chromophore similar to that of **433**), Spenser concluded³⁹¹ that there was no evidence for the existence of an aldehyde-amine (**433**) or a pseudo-base form (**432**).

The anhydro-bases are all yellow to orange in color, and their solutions in hydroxylic solvents are lighter in color than their solutions in absolute acetone, chloroform, or ether. Thus, *pyr-N*-methyl- δ -carboline anhydro-base gives rise to bands at 282, 289, 350, and 422 $m\mu$ in alkaline 95% ethanol solution, which are shifted to 289, doublet at 295 and 300, 362, and 464 $m\mu$ in ether solution.²⁶³ This has been taken as providing some tenuous support for the suggestion that structure **424a** is the more important of the two structures contributing to the resonance hybrid. The infrared spectra of *pyr-N*-methyl- δ -carboline anhydro-base and of *pyr-N*-methyl- α -carboline anhydro-base have also provided tentative *negative* evidence in support of a mesomeric structure (**424a** \leftrightarrow **424b**) in the case of the δ -anhydro-base, with the quinonoid structure **424a** making perhaps the weightier contribution to the ground state. On the other hand, the unusually high dipole moment of sempervirine (7-8D)³⁹² lends support to the conclusion that, at least for the β -carboline system, the aromatic, charge-separated form **422b** more nearly represents the properties of the anhydrobase.⁶

The determination of pK_a values of the carboline anhydro-bases has led to further speculation concerning the relative contributions of structures **a** and **b** to the ground states of the molecules. The pK_a

³⁹² K. A. Jensen, *Acta Chem. Scand.* **3**, 1447 (1949); R. Bentley and T. S. Stevens, *Nature* **164**, 141 (1949).

values of two β -carboline derivatives have been reported: 7-methoxy-1-methyl- β -carboline (harmine), pK_a 7.95³⁹³ and 7.44³⁹⁴; 7-hydroxy-1-methyl- β -carboline (harmol), pK_a 7.90.³⁹⁵

The carboline anhydro-bases are appreciably more basic than the parent carbolines. Thus a pK_a value of 10.6 was reported for *pyr-N*-methyl- β -carboline anhydro-base, for *pyr-N*-propyl- β -carboline anhydro-base, and for *pyr-N*-methyl-1-methyl- β -carboline anhydro-base³⁹¹; a pK_a value of 10.6 for sempervirine³²⁸; and values between 10.5 and 10.7 for serpentine, alstonine, and related alkaloids.¹³⁰ A study of the relative basicities of simple α -, β -, and γ -carboline anhydro-bases led to pK_a values of 7.75, 11.11, 11.20, and 10.54 for the anhydro-bases derived from *pyr-N*-methyl- α -, *pyr-N*-methyl- β -, *pyr-N*-methyl-1-methyl- β -, and *pyr-N*-methyl- γ -carbolinium iodide.³⁹⁶ These were determined by potentiometric titration at 25° of the quaternary salts in 60% aqueous ethanol. Consideration of the covalent canonical structures (421a–424a) of the anhydro-bases reveals that in the case of the α - and γ -isomers the fully aromatic nature of the benzene ring is retained, whereas in the β - and δ -isomers this ring is *o*-quinonoid. This led to the suggestion³⁹⁶ that the lower stabilization energy of the β -anhydro-base with respect to its salt results in a higher basicity of the β -isomer compared to the γ -isomer, in which both anhydro-base and salt are full benzenoid. The low basic strength of the α - as compared with the γ -anhydro-base was interpreted on the basis of two complementary factors: (a) a much increased stability of the α -anhydro-base as a result of the juxtaposition of the oppositely charged centers (in the dipolar structure 421b), and (b) a reduced stability of the α -carboline salt due to the inductive effect of the indole nitrogen attached to the same carbon atom as the positively charged pyridine nitrogen. A consideration of the basicities of 1-methyl-2-pyridonimine (435) and 1-methyl-4-pyridonimine (436) led to the suggestion that aromatic structures with charge separation more nearly represent the carboline anhydro-bases. It was argued that the 2- and 4-pyridonimines could be considered as the simplest analogs of

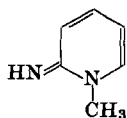
³⁹³ I. E. Orlov, *Byull. Nauch.-Issledovatel. Khim.-Farm. Inst.* 277 (1931); *Chem. Abstr.* 27, 5623 (1933).

³⁹⁴ N. A. Izmailov and M. S. Shraiber, *Farmatsiya i. Farmakol.* No. 4, 8 (1938); *Chem. Abstr.* 34, 6187 (1940).

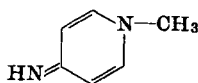
³⁹⁵ D. D. Perrin, *New Zealand J. Sci. Technol.* 38B, 688 (1957); *Chem. Abstr.* 52, 4293 (1958).

³⁹⁶ A. P. Gray, *J. Am. Chem. Soc.* 77, 5930 (1955).

the α - and γ -carboline anhydro-bases, or that the latter could be regarded as *N*-phenylpyridonimine derivatives. The pK_a values of **435** and **436** are 12.2 and 12.5, respectively.³⁹⁷ The difference (0.3 pK_a units) between the pK_a values of the pyridonimines in which the quinonoid structures make predominant contributions is much smaller than the difference between those of the α - and γ -carboline anhydro-bases (2.8 pK_a units). Though a leveling effect might, to a certain extent, account for this observation, the greater difference in basicity in the case of the α - and γ -carboline anhydro-bases was thought to be due to a major contribution of the aromatic, charge-separated forms to the structures of the anhydro-bases, and this suggestion received tenuous support from the similarity of the pK_a



[435]



[436]

values of the β - and γ -carboline anhydro-bases. The prediction³⁹⁸ that the then unknown δ -carboline anhydro-base would have a dissociation constant almost as high as that of the β -isomer was later confirmed.²⁶³ The pK_a values of the anhydro-bases prepared from the methosalts of α -, β -, and δ -carboline were redetermined spectroscopically and by potentiometric titration.²⁶³ The values obtained were as follows: α -, 7.55; β -, 10.88; and δ -, 10.77. The values for the α - and β -bases were somewhat lower than those reported earlier,³⁹⁶ that for the β -isomer being more in accord with the reported pK_a values of the β -carboline anhydro-bases quoted above.^{328, 391} The fact that the *pyr-N*-methyl- δ -carboline anhydro-base is almost as strong a base as the β -anhydro-base suggests that the quinonoid structure **424a** ($R = CH_3$) is an important contributor to its structure.³⁹⁸

From a consideration of the valence states of the nitrogen atoms in the carbolines it was argued by Paoloni and Marini-Bettòlo³⁹⁹ that it is unnecessary to consider a structure with charge separation for the

³⁹⁷ S. J. Angyal and C. L. Angyal, *J. Chem. Soc.* 1461 (1952).

³⁹⁸ That the disruption of the benzenoid structure is an important factor in the destabilization of the bases is shown by the work of Adler and Albert [*J. Chem. Soc.* 1794 (1960)] on the ionization constant of the diazaindenes where this factor is not present and the order of base strengths is 1,5- > 1,6- > 1,4- > 1,7-diazaindene.

³⁹⁹ L. Paoloni and G. B. Marini-Bettòlo, *Nature* **179**, 41 (1957).

β -carboline anhydro-bases. On the basis of LCAO calculations on the carbolines and carboline anhydro-bases, which took into account the valence states of the ring nitrogen atoms, Paoloni predicted³⁰⁹ a pK_a value of 9.83 for the δ -carboline anhydro-base, which was then unknown to him. This value was about 0.5 pK_a unit lower than that calculated for the γ -isomer (10.45) and more than 1.5 units lower than that calculated for the β -isomer (11.53). Paoloni has stressed the fact that although the calculations indicated that the base strengths decreased in the order $\beta > \gamma > \delta > \alpha$, the only conclusion that could be drawn from the numbers was that the pK_a value of the δ -anhydro-base should be somewhere between those of the α - and the β -isomers,^{309, 400} which indeed it was found to be.

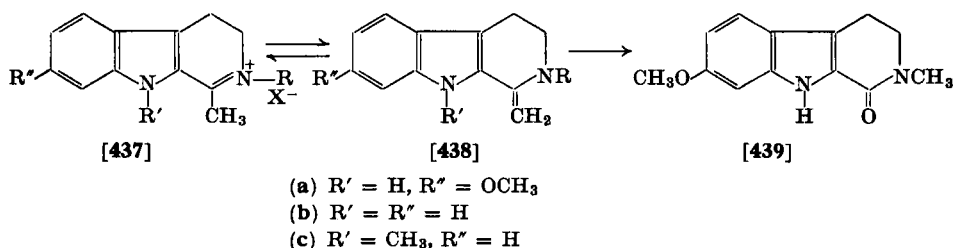
According to Paoloni³⁰⁹ the "quinonoid" formulations (a) satisfactorily account for the marked increase in basicities and in dipole moments and for the bathochromic shift of the absorption spectra of the anhydro-bases as compared to those of the quaternary carbolinium salts, if the valence states of the nitrogens are taken into account. He concludes that it is, therefore, unnecessary to represent the anhydro-bases as resonance hybrids of classical "quinonoid" structures (a) and dipolar structures (b); the former being sufficient to explain on their own the observed properties of these bases. The formulation of the anhydro-bases as quinonoid structures taking into account the valence states of the nitrogen atoms—*ind*- $N[s^2, p(xyz)]$ and *pyr*- $N[s, p(x^2yz)]$ —favored by Paoloni on the basis of molecular orbital calculations, and their alternative valence bond formulation as resonance hybrids of quinonoid and dipolar structures, originally put forward by Armit and Robinson²⁶⁹ and accepted by organic chemists in general, are not contradictory. The latter representation conveys to the organic chemist a clearer picture of the "compromise between the tendency to form the aromatic sextet and that to neutralize the charges" and of the probable chemical and physical properties of the molecules than the former, from which these properties are not *immediately* obvious. The relative merits of valence-bond and molecular orbital representations are, however, beyond the scope of this review.

B. 3,4-DIHYDRO- β -CARBOLINE ANHYDRO-BASES

Anhydro-bases derived from 3,4-dihydro- β -carboline derivatives have received much less attention than those of the carboline series.

⁴⁰⁰ L. Paoloni, personal communication (1962).

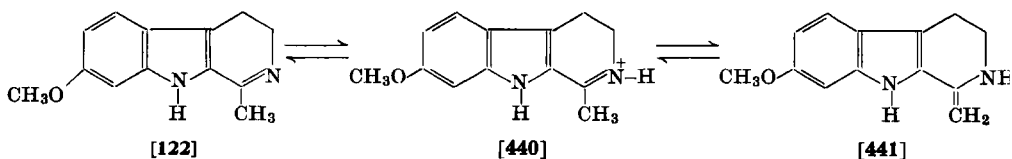
pyr-N-Methylharmalinium salts (**437a**; $R = CH_3$) on treatment with alkali yield an anhydro-base, which was formulated as **438a** ($R = CH_3$) because of its facile oxidation to 2-methyl-1-oxo-1,2,3,4-tetrahydro- β -carboline (**439**).¹⁵¹ Analogous anhydro-bases (**438**) from *pyr-N*-ethylharmalinium iodide (**437a**; $R = C_2H_5$),³¹² from *pyr-N*-methyl- (**437b**; $R = CH_3$) and *pyr-N*-*n*-propyl-1-methyl-3,4-dihydro- β -carbolinium iodide (**437b**; $R = C_3H_7$), and from *pyr-N*-methyl-1,9-dimethyl-3,4-dihydro- β -carbolinium iodide (**437c**; $R = CH_3$) have also



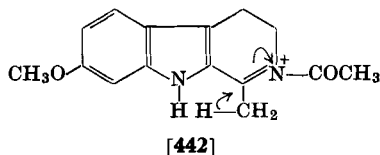
been prepared.³⁵⁴ The anhydro-bases are amorphous solids which are difficult to purify, but are colorless when pure. On treatment with acid they revert to the quaternary 3,4-dihydro- β -carbolinium structure from which they are derived. This is in accord with the known behavior of anhydro-bases in general.

The ultraviolet absorption spectra of the anhydro-bases in acid solution or in protic solvents are those of the 3,4-dihydro- β -carbolinium ion (λ_{\max} 355 $m\mu$ for **438b** and **438c**). In alkaline solution and in non-ionizing solvents absorption at a shorter wavelength (λ_{\max} 315 $m\mu$) is observed. In general, solutions of the anhydro-bases in acid and in protic solvents are more deeply colored than their solutions in basic or in non-ionizing media.

It has been postulated that harmaline itself "may under certain conditions consist of an equilibrium mixture of the isomeric structures **122** and **441**, with the former strongly predominating".¹ Both forms are regarded as existing in equilibrium with the harmalinium cation (**440**), from which the former may be derived by deprotonation at the

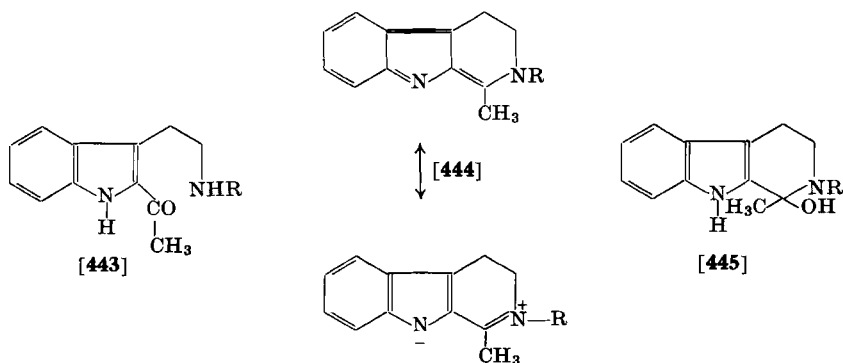


pyr-N, the latter by deprotonation at the 1-methyl group.²¹⁰ It has been stated¹ that the synthesis of harmaline by dehydration of 1-hydroxymethyl-7-methoxy-1,2,3,4-tetrahydro- β -carboline²⁶ (cf. Section III, C, 2, b) confirms its tautomeric nature, which is also indicated by the fact that harmaline forms a *pyr-N*-acetyl derivative (cf. Section IV, B, 2). It is unnecessary, however, to postulate the existence of such an equilibrium. In the acid-catalyzed dehydration,



the expected intermediate, a protonated enamine, would spontaneously rearrange to the immonium salt.⁴⁰¹ In the acylation reaction the probable intermediate, an unstable quaternary acyldihydropyridinium salt (442), analogous in structure to similar intermediates in the pyridine series,⁴⁰² is subsequently stabilized by deprotonation at the 1-methyl group, which can occur without disruption of benzenoid conjugation, rather than at the *ind-N* atom, which would be accompanied by loss of aromaticity.

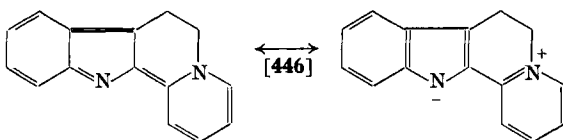
In addition to the enamine formulation of the anhydro-bases as 2-methylene-1,2,3,4-tetrahydro- β -carboline derivatives (438), three



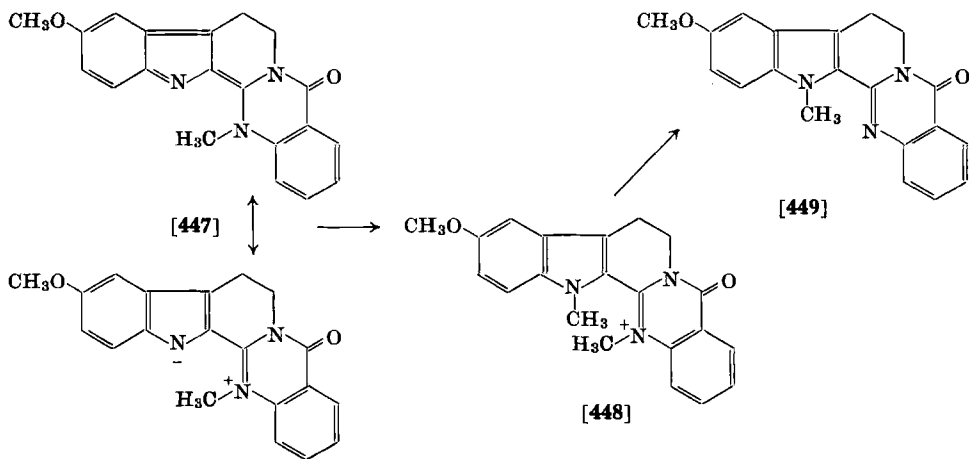
⁴⁰¹ N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.* **76**, 2781 (1954); G. Opitz, H. Hellmann, and W. Schubert, *Ann. Chem.* **623**, 112, 117 (1959).

⁴⁰² R. A. Barnes, in "Pyridine and its Derivatives" (E. Klingsberg, ed.), Part 1, p. 1. Interscience, New York, 1960.

alternative structures must be considered. The first of these, the ketoamine structure **443**, is of a type which has been discussed in connection with anhydro-bases of the dihydroisoquinoline series and was rejected since no carbonyl absorption was detectable in the infrared spectra of the compounds.³⁵⁴ As a second alternative the compounds can be formulated as anhydro-bases (**444**) of the "carboline type"; formation of these requires deprotonation at the indole nitrogen. Since the *ind-N*-methyl derivative **437c** gave rise to an anhydro-base which has



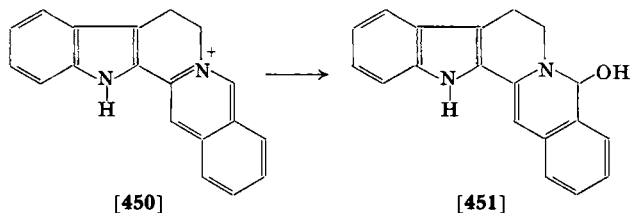
properties analogous to those of compounds derived from the *ind-N*-unsubstituted quaternary 3,4-dihydro- β -carbolinium salts, this alternative may also be rejected. Formation of a "carboline-type" anhydro-base has, however, been reported in the case of a complex quaternary 3,4-dihydro- β -carbolinium salt (**446**).²¹² A related structure (**447**) was assigned to hortiamine.³⁴⁹ Like " β -carboline-type" anhydro-bases, the latter compound undergoes alkylation at the *ind-N* to yield a quaternary salt (**448**), which, on pyrolysis, suffers demethylation at the cationoid nitrogen atom to yield the *ind-N*-methyl derivative **449**.



Formation of a quinonoid "carboline-type" anhydro-base requires loss of resonance stabilization of the indole moiety. In the carboline anhydro-bases this is counterbalanced by the preservation of a 6π system in the hetero ring. No such balancing factor is present in the case of 3,4-dihydro- β -carboline derivatives. Formation of the exocyclic anhydro-base in the latter case preserves benzenoid resonance. It is noteworthy that in the two cases where formation of a carboline-type anhydro-base was reported in dihydro derivatives additional aromatic conjugation is present.

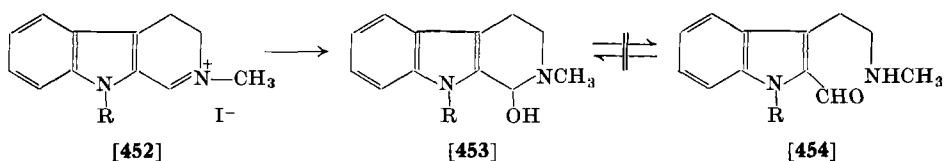
The third structural possibility, the formulation of the compounds as pseudo-bases (**445**) was eliminated in the case of the anhydro-bases derived from *pyr-N*-alkyl-1-methyl-3,4-dihydro- β -carbolinium salts on the basis of their ultraviolet absorption spectra. A structure such as **445** demands indole-type absorption ($\lambda_{\max} \sim 280 \text{ m}\mu$) which was not encountered in the spectra of the anhydro-bases under discussion. This is in accord with general experience. Pseudo-bases are generally found only when dehydration to anhydro-bases is structurally impossible.^{402a} Indole-type absorption was indeed found in the case of the product obtained by treatment of 3,4-dihydro- β -carboline methiodide (**452**; R = H) with alkali.¹⁹² In acid solution this compound gave the expected absorption ($\lambda_{\max} 355 \text{ m}\mu$). In alkaline solution, however, an indole-type absorption ($\lambda_{\max} 285 \text{ m}\mu$) was observed. On this basis formulation of the product as a derivative of 2-formylindole (**454**) ($\lambda_{\max} 315 \text{ m}\mu$) was rejected. Although the indole-type absorption is in accord with the pseudo-base structure **453** (R = H), the elemental analysis and molecular weight were not compatible with this formulation and the product was regarded as a dimeric anhydro-base (**455**).

^{402a}The dihydro- β -carbolinium salt **450** has been reported to form a pseudo-base (**451**) on treatment with alkali.²¹³ It is of interest that the $\text{p}K_a$ value for this compound^{197, 403} was found to be 11.7, i.e., of the same order of magnitude as those of the β -carboline anhydro-bases.

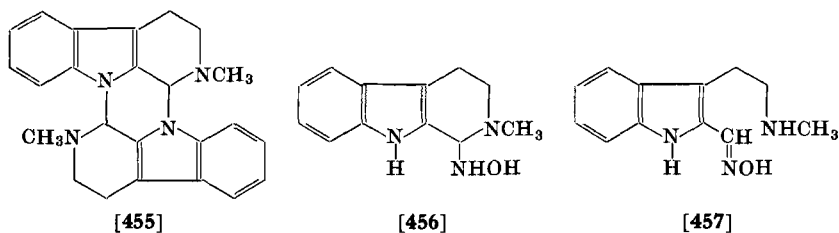


⁴⁰³ G. A. Swan, *J. Chem. Soc.* 1539 (1950).

This dimeric formulation also accounts for the thermal disproportionation of the compound into a mixture of 2-methyl-1,2,3,4-tetrahydro- β -carboline and 2-methyl- β -carboline anhydro-base. Normal pseudo-base formation (**453**; $R = CH_3$) takes place in the case of 9-methyl-3,4-dihydro- β -carboline methiodide (**452**; $R = CH_3$). Neither the dimeric anhydro-base nor the 9-methyl pseudo-base undergo a base-catalyzed disproportionation reaction to give the 1,2,3,4-tetrahydro- and the 1-oxo-1,2,3,4-tetrahydro- β -carboline in a manner analogous



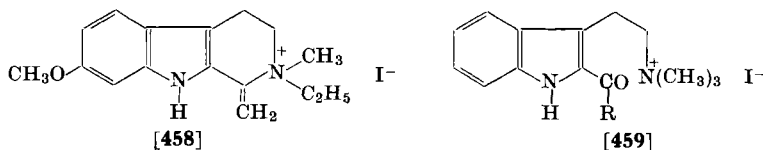
to the conversion of hydrastinine into hydrohydrastinine and oxohydrastinine.⁴⁰⁴ Both compounds form condensation products with hydroxylamine. These did not show absorption in the infrared region of the spectrum characteristic of an oxime group and must, therefore, be formulated as 1-hydroxylamino-1,2,3,4-tetrahydro- β -carbolines (**456**). Their ultraviolet absorption spectrum was, however, similar to that of 2-formylindole. This would appear to favor their existence in solution as derivatives of the oxime of the indole-2-aldehyde **457**.



Alkylation of the anhydro-bases derived from 3,4-dihydro- β -carboline and 1-methyl-3,4-dihydro- β -carboline takes place at the *pyr-N* and is accompanied by ring cleavage. It was believed that alkylation of the anhydro-bases derived from 7-methoxy-1-methyl-3,4-dihydro- β -carboline alkiodides occurred at the *pyr-N* to give quaternary salts of type **458**.³¹² It has now been shown, however, that methylation of the anhydro-base **438b** ($R = CH_3$) actually gives the

⁴⁰⁴ M. Freund and W. Will, *Ber.* **20**, 2400 (1887).

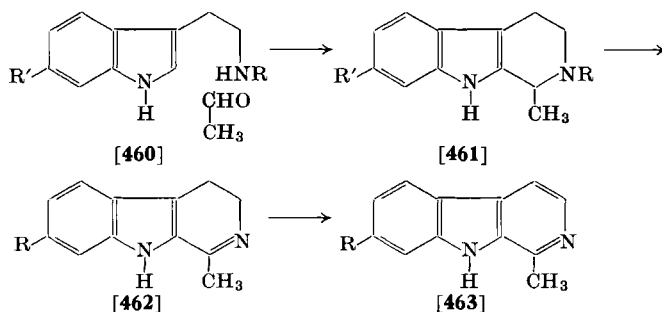
quaternary ammonium salt of 2-acetyltryptamine (**459**; $R = CH_3$).³⁵⁴ Similarly, **459** ($R = H$) is obtained by methylation of **455**.¹⁹² Alkylation at the enamine carbon atom of the 1-methylene-1,2,3,4-tetrahydro- β -carboline derivatives (**438**), although not wholly excluded, appears to be of minor importance only.



VII. Biogenesis and Biosynthesis of Naturally Occurring Carbolines

As long ago as 1919, Perkin and Robinson¹⁵⁰ noted that harmine, harmaline, and harmalol, the only naturally occurring carboline derivatives known at that time, were structurally related to tryptophan and suggested that the bases were biogenetically derived from this amino acid by way of a hypothetical hydroxytryptophan. Indeed they adduced this chemical relationship as one of the strongest arguments in favor of the structural formulation of these alkaloids as β -carbolines, thereby anticipating by some thirty years a line of reasoning which, within the last decade, has been fruitfully employed in the structural elucidation of complex natural products.

These authors formulated the major steps in the biogenesis of the harmala bases as a condensation of a tryptamine derivative (**460**) with acetaldehyde to yield a 1,2,3,4-tetrahydro- β -carboline (**461**), which on oxidation in two stages would give harmaline (**462**; $R = OCH_3$) and then harmine (**463**; $R = OCH_3$).



Guided by this hypothetical relationship Perkin and Robinson² predicted and proved that an artifact obtained by Hopkins and Cole⁴⁰⁵

⁴⁰⁵ F. G. Hopkins and S. Cole, *J. Physiol. (London)* **29**, 451 (1903).

by oxidation of tryptophan with ferric chloride was 1-methyl- β -carboline (**463**; R = H) and expressed the view that this compound owed its formation to a biogenetically patterned synthesis in which the tryptophan had reacted with a two-carbon unit derived either from alanine present in the crude sample² or from the solvent used in the reaction.²²¹

Following up this idea they synthesized β -carboline and 1-methyl- β -carboline by reaction of tryptophan with formaldehyde and acetaldehyde, respectively, under oxidizing conditions.²²¹ The steps of this biogenetically patterned synthesis have been repeatedly studied and are fully discussed in Sections III, A, 1, a and III, E, 2, a, i. The formation of 1,2,3,4-tetrahydro- β -carbolines as the initial step in the biogenesis of β -carboline alkaloids, by reaction of tryptophan or tryptamine or the corresponding hydroxylated derivatives with aldehydes or α -keto acids, derivable from α -amino acids, is a widely held concept. Two lines of circumstantial evidence favor this hypothesis. First, a number of simple 1,2,3,4-tetrahydro- β -carboline derivatives have been found to occur naturally. 1-Methyl-1,2,3,4-tetrahydro- β -carboline (**461**; R' = R = H; eleagnine) has been isolated from *Elaeagnus angustifolia*,^{124, 406} *Pentalostyles labicheoides*,³⁶⁵ and *Leptactina densiflora*,⁴⁰⁷ and 7-hydroxy-1-methyl- (**461**; R' = OH, R = H) and 7-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydro- β -carboline (**461**; R' = OH, R = CH₃) from *Elaeagnus angustifolia*.¹²⁵ 7-Methoxy-1-methyl-1,2,3,4-tetrahydro- β -carboline (tetrahydroharmine, leptafflorine; **461**, R' = OCH₃, R = H) has been obtained from *Leptactina densiflora*⁴⁰⁷ and also from *Banisteria caapi*, where it occurs together with harmine and harmaline.⁴⁰⁸

Evidence has been put forward that 6-methoxy-1-methyl-1,2,3,4-tetrahydro- β -carboline may be a component of animal tissues and may be identical with "adrenoglomerulotrophine," a factor controlling aldosterone secretion, which is found in the pineal gland^{24, 409} where it occurs together with 5-hydroxytryptamine (serotonin) and 5-methoxy-*N* β -acetyltryptamine (melatonin).⁴¹⁰ This has been confirmed by a comparison of the synthetic material with the

⁴⁰⁶ P. S. Massagetov, *Zh. Obshch. Khim.* **16**, 139, 775 (1946).

⁴⁰⁷ R. R. Paris, F. Percheron, J. Mainil, and R. Goutarel, *Bull. Soc. Chim. France* 780 (1957).

⁴⁰⁸ F. A. Hochstein and A. M. Paradies, *J. Am. Chem. Soc.* **79**, 5737 (1957).

⁴⁰⁹ G. L. Farrell and W. M. McIsaac, *Arch. Biochem. Biophys.* **94**, 543 (1961).

⁴¹⁰ A. B. Lerner, J. D. Case, and Y. Takahashi, *J. Biol. Chem.* **235**, 1992 (1960).

hormone.^{410a} It was suggested that in certain psychotic conditions melatonin might give rise to 6-methoxy-1-methyl-3,4-dihydro- β -carboline by a metabolic analog of the Bischler-Napieralski reaction.⁴¹¹

1,2-Dimethyl-1,2,3,4-tetrahydro- β -carboline (leptocladine) (**461**; $R' = H$, $R = CH_3$) was recognized as a constituent of *Arthrophytum leptocladum*,^{23, 412} where it is found together with N_β -methyltryptamine (dipterine; **460**, $R' = H$, $R = CH_3$), its probable biogenetic precursor. The isolation, from the same source, of a base, claimed to be 2-methyl-1,2,3,4-tetrahydro- β -carboline, has been reported,⁴¹³ but no direct structural evidence for this identity was presented. The above taxonomical evidence strengthens the concept that 1,2,3,4-tetrahydro- β -carbolines represent a stage in β -carboline biogenesis.

The second line of circumstantial evidence quoted in support of this hypothesis is the ready formation of 1,2,3,4-tetrahydro- β -carboline derivatives under "pseudo-physiological" conditions of temperature, pH, and concentration. Tryptamine and aldehydes,^{20, 28, 414} tryptamine and α -keto acids,^{28, 69} and tryptophan and aldehydes^{40, 44} condense at room temperature in a Pictet-Spengler type intramolecular Mannich reaction in the pH range 5.2–8.0 (cf. Section III, A, 1, a). It was argued⁴¹⁵ that experiments of this type serve as models for biochemical reactions and may be used in evidence.

Partial dehydrogenation of a tetrahydro- β -carboline derivative has been postulated^{150, 365, 416} to account for the origin of 7-hydroxy-1-methyl-3,4-dihydro- β -carboline (harmalol; **462**, $R = OH$), occurring in *Peganum harmala*,^{355, 417} and the corresponding *O*-methyl ether harmaline (**462**; $R = OCH_3$), obtained from the same plant⁴¹⁸ as well as from *Banisteria caapi*,^{408, 419} and further loss of hydrogen has been postulated for that of 7-hydroxy-1-methyl- β -carboline (harmol; **463**,

^{410a} J. Supniewski and S. Miszkal, *Bull. Acad. Polon. Sci., Ser. Sci. Biol.* **11**, 309 (1963); *Chem. Abstr.* **60**, 2918 (1964).

⁴¹¹ W. M. McIsaac, P. A. Khairallah, and I. H. Page, *Science* **134**, 674 (1961).

⁴¹² N. K. Yurashevski, *Zh. Obshch. Khim.* **9**, 595 (1939).

⁴¹³ T. F. Platonova, A. D. Kuzovkov, and P. S. Massagetov, *J. Gen. Chem. USSR (Eng. Transl.)* **28**, 3159 (1958).

⁴¹⁴ C. Schöpf and H. Bayerle, *Ann. Chem.* **513**, 190 (1934).

⁴¹⁵ C. Schöpf, *Angew. Chem.* **50**, 779, 797 (1937).

⁴¹⁶ M. Guggenheim, "Die Biogenen Amine," p. 587. Karger, Basel, 1951.

⁴¹⁷ A. Schipper and O. H. Volk, *Deut. Apotheker-Ztg.* **100**, 255 (1960); *Chem. Abstr.* **55**, 16913 (1961).

⁴¹⁸ F. Goebel, *Ann. Chem.* **38**, 363 (1841).

⁴¹⁹ A. P. Orekhov, *Byull. Nauch.-Issledovatel. Khim.-Farm. Inst.* **3** (1930); *Chem. Abstr.* **26**, 5699 (1932).

R = OH) (*Passiflora incarnata*,⁴²⁰ *Zygophyllum fabago*⁴²¹), 7-methoxy-1-methyl- β -carboline (harmine, telepathine, yageine, banisterine; **463**, R = OCH₃) (*Peganum harmala*,²⁹⁰ *Passiflora incarnata*,⁴²⁰ *Banisteria caapi*,^{408, 422} *Zygophyllum fabago*,⁴²¹ *Banisteriopsis inebrians*,⁴²³ *Cabi paraensis*⁴²⁴), 1-methyl- β -carboline (**463**, R = H; harman, aribine, loturine, passiflorine) (*Abrariba rubra*,⁴²⁵ *Symplocos racemosa*,⁴²⁶ *Passiflora incarnata*,^{420, 427} *Zygophyllum fabago*⁴²¹), and 1,2-dimethyl- β -carboline anhydro-base (**246**; R = R' = CH₃; melinonine F) (*Strychnos melinoniana*⁴²⁸).

Whereas oxidation of 1-methyl-1,2,3,4-tetrahydro- β -carboline (**461**; R = R' = H) itself does not take place readily, oxidation of 1-methyl-1,2,3,4-tetrahydro- β -carboline-3-carboxylic acid (**17**; R = CH₃) with acid dichromate gives 1-methyl- β -carboline (**463**; R = H) in high yield. Modelled on this finding, the biogenetic origin of 1-methyl- β -carboline from tryptophan (**15**) by way of the tetrahydro- β -carboline-3-carboxylic acid, without the intermediate formation of a 3,4-dihydro- β -carboline, has been proposed.⁴²⁹ This sequence cannot account for the biogenetic origin of 1-methyl- β -carboline-3-carboxylic acid (**466**), which was recently isolated from *Aspidosperma polyneuron*.⁴³⁰

⁴²⁰ J. Lutomski, *Biul. Inst. Roslin Leczniczych* **5**, 182 (1959) [*Chem. Abstr.* **54**, 16751 (1960)]; **6**, 209 (1960) [*Chem. Abstr.* **55**, 21479 (1961)]; J. Lutomski and T. Wrocinski, *Biul. Inst. Roslin Leczniczych* **6**, 176 (1960) [*Chem. Abstr.* **55**, 6785 (1961)].

⁴²¹ B. Borkowski, *Biul. Inst. Roslin Leczniczych* **5**, 158 (1959); *Chem. Abstr.* **54**, 15844 (1960).

⁴²² F. Elger, *Helv. Chim. Acta* **11**, 162 (1928); O. Wolfes and K. Rumpf, *Arch. Pharm.* **266**, 188 (1928); A. L. Chen and K. K. Chen, *Quart. J. Pharm. Pharmacol.* **12**, 30 (1939) [*Chem. Abstr.* **33**, 5125 (1939)].

⁴²³ F. D. O'Connell and E. V. Lynn, *J. Am. Pharm. Assoc.* **42**, 753 (1953); *Chem. Abstr.* **48**, 2988 (1954).

⁴²⁴ W. B. Mors and P. Zaltzmann, *Bol. Inst. Quim. Agr. (Rio de Janeiro)* No. **34**, 17 (1954); *Chem. Abstr.* **49**, 14906 (1955).

⁴²⁵ R. Rieth, *Ann. Chem.* **120**, 247 (1861); E. Späth, *Monatsh. Chem.* **40**, 351 (1919).

⁴²⁶ O. Hesse, *Ber.* **11**, 1542 (1878); E. Späth, *Monatsh. Chem.* **41**, 401 (1920).

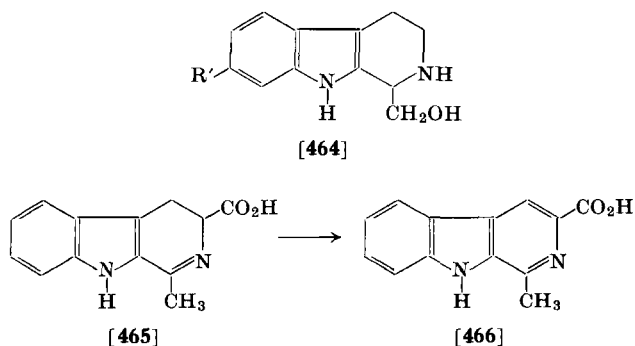
⁴²⁷ R. Neu, *Arzneimittel-Forsch.* **4**, 292 (1954) [*Chem. Abstr.* **48**, 9018 (1954)]; **4**, 601 (1954) [*Chem. Abstr.* **49**, 2679 (1955)]; **6**, 94 (1956) [*Chem. Abstr.* **50**, 14183 (1956)].

⁴²⁸ E. Bächli, C. Vamvacas, H. Schmid, and P. Karrer, *Helv. Chim. Acta* **40**, 1167 (1957).

⁴²⁹ R. Robinson, *J. Chem. Soc.* 1079 (1936); Intern. Congr. Biochem., 1st Congr., Cambridge, Engl. p. 32 (1949).

⁴³⁰ L. D. Antonaccio and H. Budzikiewicz, *Monatsh. Chem.* **93**, 962 (1962).

The comparative rarity of 3,4-dihydro- β -carbolines in plants has been noted, and it was argued that if a stepwise oxidation sequence represented the biogenetic origin of dihydro- β -carbolines and β -carbolines, the former might be expected to accompany the latter more frequently. An alternative hypothesis for the nonoxidative biogenetic origin of 1-methyl-3,4-dihydro- β -carbolines was therefore advanced, involving the condensation of a tryptamine derivative with glycolaldehyde to yield a 1-hydroxymethyl-1,2,3,4-tetrahydro- β -carboline (**464**), dehydration of which gives rise to the corresponding 1-methyl-3,4-dihydro- β -carboline (**462**).²⁶



A similar reaction sequence starting from tryptophan yields 1-methyl-3,4-dihydro- β -carboline-3-carboxylic acid (**465**).²⁶ This compound has been shown to undergo photochemical oxidation to 1-methyl- β -carboline-3-carboxylic acid (**466**).²⁰⁸ Such a sequence of events may account for the biogenetic origin of the amino acid **466**.

β -Carboline derivatives in various oxidation states have been isolated from a number of natural sources as artifacts. β -Carboline has been obtained from charred insects,⁴³¹ β -carboline and 1-methyl- β -carboline have been found in cigarette smoke,⁴³² and the formation of tetrahydro- β -carboline derivatives has been shown to be responsible for the destruction of tryptophan in acid hydrolyzates of proteins.⁸⁵

The golden-yellow fluorescence observed when enterochromaffin cells are fixed in formaldehyde has been related to their content of

⁴³¹ A. Ogata, K. Takagi, A. Mizutani, and S. Iijima, *J. Pharm. Soc. Japan* **66**, 44 (1946); *Chem. Abstr.* **44**, 1650 (1950).

⁴³² E. H. Poindexter, Jr., and R. D. Carpenter, *Chem. Ind. (London)* 176 (1962); *Phytochemistry* **1**, 215 (1962).

5-hydroxytryptamine,⁴³³ and it has been postulated that the fluorescence was due to β -carboline formation.⁴³⁴ This view has been questioned.⁴³⁵

It has been suggested that the blue-green fluorescence produced when 5-hydroxytryptamine is treated with ninhydrin is due to the formation of β -carboline derivatives⁴³⁶ and that a brilliant orange-red color, which is produced when histochemical sections which have been fixed in formalin are heated after treatment with ninhydrin and acetic acid, is due to the conversion of tryptamine derivatives into 1,2,3,4-tetrahydro- β -carboline.⁴³⁷

Whatever the detailed biogenetic steps, there is almost general agreement that β -carboline derivatives originate in living systems from tryptophan or tryptamine.

The only divergent opinion is that of Wenkert,⁴³⁸ who postulates that the harmala bases are derived directly from carbohydrate precursors by way of an anthranilate-erythrose-derived intermediate and not by way of tryptophan or tryptamine. This interesting alternative hypothesis, which is based almost entirely on structural arguments, was put forward as one aspect of a general carbohydrate hypothesis of alkaloid biogenesis. In a few cases where the alternative hypotheses are amenable to direct differential experimental test^{439, 440} the carbohydrate hypothesis has not been substantiated. Whether or not it is applicable to the biogenesis of the harmala bases has not yet been investigated by biosynthetic experiment.

The biogenetic origin of β -carboline systems with extended rings has been repeatedly discussed. Almost invariably tryptophan or tryptamine is assumed to give rise to the major portion of the β -carboline nucleus. Attention in these discussions was focused on the elaboration of the non-carboline portion of these molecules. Discussion of these

⁴³³ D. M. Shepherd, G. B. West, and V. Ersparmer, *Nature* **172**, 357 (1953).

⁴³⁴ R. Barter and A. G. Everson, *J. Pathol. Bacteriol.* **69**, 25 (1955); *Chem. Abstr.* **49**, 16133 (1955).

⁴³⁵ R. D. Lillie, *J. Histochem. Cytochem.* **5**, 188 (1957); *Chem. Abstr.* **51**, 13042 (1957).

⁴³⁶ J. B. Jepson and B. J. Stevens, *Nature* **172**, 772 (1953).

⁴³⁷ J. Holcenberg and E. P. Benditt, *Lab. Invest.* **10**, 144 (1961); *Chem. Abstr.* **55**, 10552 (1961).

⁴³⁸ E. Wenkert, *Experientia* **15**, 165 (1959).

⁴³⁹ E. Leete, S. Ghosal, and P. N. Edwards, *J. Am. Chem. Soc.* **84**, 1068 (1962).

⁴⁴⁰ J. R. Gear and I. D. Spenser, *Can. J. Chem.* **41**, 783 (1963); A. R. Battersby and D. J. McCaldin, *Proc. Chem. Soc.* 365 (1962).

ideas is beyond the scope of this review, but key references are given.^{383, 441-443} The alternative carbohydrate hypothesis of biogenesis has also been brought to bear on these extended systems.^{438, 444} Based on considerations of this type, biogenetically patterned syntheses⁵⁷ and syntheses under "pseudo-physiological" conditions^{68, 191, 415} have been carried out.

Whereas β -carboline derivatives abound in nature, other carbolines are virtually unknown in living systems. The only exception is a benz- δ -carboline derivative, cryptolepine (**78**).¹⁴³ Two alternative biogenetic schemes, one based on tryptophan and *o*-methylaminobenzaldehyde,⁴⁴⁵ the other based on an anthranilic acid-erythrose adduct and a second anthranilic acid unit,⁴³⁸ have been proposed. The origin of α -carboline, which has been isolated from coal tar oil⁴⁴⁶ has not been considered.

In contrast to the wealth of biogenetic speculation and model experimentation, none of which has direct bearing on actual biochemical events in the synthesis of β -carbolines in their natural habitat, very few biosynthetic investigations have been carried out. As predicted, radioactivity from 2-¹⁴C-tryptophan was incorporated into carbon atom-3 of the 1,2,3,4,4a,9a-hexahydro- β -carboline moiety of ajmaline^{378, 447} and into carbon atom-3 of the β -carbolinium segment of serpentine.⁴⁴⁸ It has also been reported⁴⁴⁹ that labelled tryptophan gave radioactive β -carboline derivatives in *Peganum harmala*. The indications are that classical biogenetic predictions correctly foreshadowed the gross events in the biosynthesis of the β -carboline

⁴⁴¹ G. Barger and C. Scholz, *Helv. Chim. Acta* **16**, 1343 (1933); G. Barger, *Cong. Intern. Quim. Pura Ap.*, **9**, Madrid 1934, 177 (1935); *Bull. Soc. Chim. Biol.* **20**, 685 (1938).

⁴⁴² R. Goutarel, M.-M. Janot, V. Prelog, and W. I. Taylor, *Helv. Chim. Acta* **33**, 150 (1950); E. Schlittler and W. I. Taylor, *Experientia* **16**, 244 (1961).

⁴⁴³ R. Robinson, "Structural Relations of Natural Products," pp. 108, 111, 119. Clarendon Press, Oxford, 1955.

⁴⁴⁴ E. Wenkert, E. W. Robb, and N. V. Bringi, *J. Am. Chem. Soc.* **79**, 6570 (1957); E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.* **81**, 1474 (1959); E. Wenkert, *J. Am. Chem. Soc.* **84**, 98 (1962).

⁴⁴⁵ R. Robinson, "The Structural Relations of Natural Products," p. 106, errata. Clarendon Press, Oxford, 1955.

⁴⁴⁶ O. Kruber and R. Oberkobusch, *Chem. Ber.* **86**, 309 (1953).

⁴⁴⁷ E. Leete, *Chem. Ind. (London)* 692 (1960).

⁴⁴⁸ E. Leete, *Tetrahedron* **14**, 35 (1961).

⁴⁴⁹ D. Gröger and H. Simon, quoted by K. Mothes, *Wiss. Z. Martin Luther Univ. Halle* **10**, 1149 (1961).

nucleus. The details of the biosynthetic pathways involved remain to be elucidated.

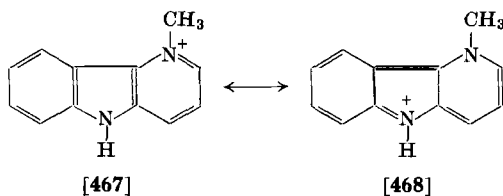
VIII. Spectra

The ultraviolet absorption spectra of carboline derivatives have been repeatedly recorded. Since the basic *pyr-N* in the carbolines and in 3,4-dihydro- β -carbolines is part of a conjugated system, protonation affects the electronic absorption spectra significantly. It is unfortunate therefore that the spectra of the protonated, as well as those of the unprotonated, species have not been reported in all instances. Protonation leads to a bathochromic shift of 20–30 m μ . This is illustrated by the absorption of β -carboline,³⁹¹ 1-methyl- β -carboline,^{450, 451} 7-methoxy-1-methyl- β -carboline,⁴⁵² and the salts of these compounds.

The ultraviolet spectra of α -,⁴⁵³ γ -,⁸⁶ and δ -carboline²⁶³ have been recorded, as well as those of a number of benz-carbolines (2,3-benz- α -,⁴⁵⁴ 2,3-benz- δ -,^{143, 454} and 3,4-benz- β -carboline⁴⁵⁵) and quaternary benzcarbolinium salts (2,3-benz- γ -⁸⁶ and 1,2-benz- β -carbolinium ion^{142, 212, 213}). Whereas the spectra of α - and β -carboline are quite similar,⁴⁵³ both differ substantially from that of δ -carboline.²⁶³

ind-N-Alkylation results in a bathochromic shift of 10 m μ in the β -⁴⁵ and δ -carboline spectra,²⁶³ and *ind-N*- and *pyr-N*-alkylation causes a similar shift in the spectrum of the quaternary β -carbolinium ion.^{391, 428, 451, 456}

This effect of *pyr-N*-alkylation on the spectra of the carbolines,



⁴⁵⁰ H. Schmid, E. Ebnöther, and P. Karrer, *Helv. Chim. Acta.* **33**, 1486 (1950).

⁴⁵¹ Raymond-Hamet, *Compt. Rend.* **232**, 507 (1951).

⁴⁵² A. D. Rosenfeld and D. G. Kolesnikov, *Ber.* **69**, 2022 (1936).

⁴⁵³ L. Horner, *Ann. Chem.* **540**, 73 (1939).

⁴⁵⁴ G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.* 1658 (1952).

⁴⁵⁵ G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.* 671 (1951).

⁴⁵⁶ F. Pruckner and B. Witkop, *Ann. Chem.* **554**, 127 (1943).

which is most pronounced in the case of δ -carboline and smallest in the case of α -carboline, has been discussed in the δ -series in terms of structures such as **467** and **468**.²⁶³ A bathochromic shift is also caused by the introduction of methoxyl groups into the 6- or 7-position of 1-methyl- β -carboline. Introduction of a methoxyl group into the 5- or 8-position did not give this effect.⁴⁵

The bathochromic shift which results when a quaternary *ind-N*-unsubstituted *pyr-N*-alkyl- α -,⁶ β -,^{27, 280, 391} γ -,⁸⁶ or δ -carbolinium salt²⁶³ is converted into the corresponding anhydro-base is referred to in Section VI, A.

The ultraviolet absorption spectra of 3,4-dihydro- β -carboline derivatives exhibit a dependence on pH similar to that shown by the spectra of the fully aromatic compounds. 3,4-Dihydro- β -carboline¹⁹² and 1-methyl-^{26, 451} and 7-methoxy-1-methyl-3,4-dihydro- β -carboline^{26, 452} serve as examples. The quaternary 3,4-dihydro- β -carbolinium salts obtained on *pyr-N*-alkylation of these dihydro- β -carbolines^{192, 354, 456} show a bathochromic shift of 5 m μ compared to the spectrum of the parent compound in acid solution. Anhydro-base formation in compounds of this type leads to a hypsochromic shift.^{192, 204} A strong bathochromic effect results from the introduction of a methoxyl group into the 7-position of the nucleus.²⁶

Ultraviolet spectra of a 1,2-dihydro- γ -carboline derivative⁸⁶ and of a number of quaternary 1,2-benz-3,4-dihydro- β -carbolinium derivatives and of the anhydro-bases derived from them^{212, 213} have been recorded. It is noteworthy that introduction of a 6-hydroxyl group does not affect the spectrum of the 1,2-benz-3,4-dihydro- β -carbolinium ion, whereas introduction of a 7-methoxyl group leads to a bathochromic shift of 20 m μ .²¹⁴

The spectrum of 1,2,3,4-tetrahydro- β -carboline is essentially unaffected by changes in pH⁴⁵¹ and is substantially that of a 2,3-disubstituted indole.⁴⁵⁷

The spectra of a number of 1-oxo-1,2-dihydro- β -carboline derivatives²²³ and 1-oxo-1,2,3,4-tetrahydro- β -carboline derivatives^{175, 192} have also been recorded.

The intense fluorescence of β -carbolinium salts has been repeatedly noted (see, e.g., ref. 3). The wavelengths for maximum activation and emission of fluorescence have been determined for harmine,⁴⁵⁸

⁴⁵⁷ See, e.g., B. G. Edward, *Arch. Biochem.* **21**, 103 (1949).

⁴⁵⁸ S. Udenfriend, D. E. Duggan, B. M. Vasta, and B. B. Brodie, *J. Pharmacol. Exp. Therap.* **120**, 26 (1957); *Chem. Abstr.* **51**, 18473 (1957).

harmaline, and β -carboline,⁴⁵⁹ and the fluorescence spectra of 1-methyl- β -carboline and 1-methyl- and 7-methoxy-1-methyl-1,2,3,4-tetrahydro- β -carboline as well as a number of other derivatives have also been determined.⁴⁶⁰

The β -carboline ring system appears to be reasonably stable to electron impact and has been detected in mass spectroscopic studies of alkaloids containing an extended 1,2,3,4-tetrahydro- β -carboline system. Depending on the mode of ring extension, such alkaloids yield either β -carboline fragments (e.g. sarpagine,^{461, 461a} polynuridine,⁴⁶² and voachalotine and related compounds⁴⁶³) or other aromatic fragments (e.g. eburnamine⁴⁶⁴).

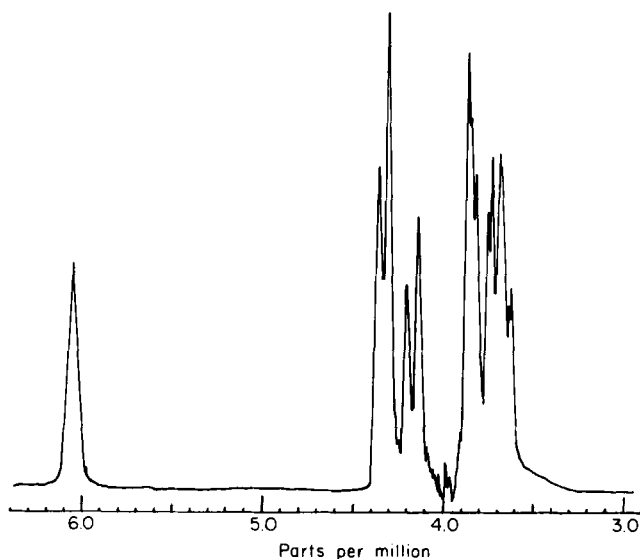


FIG. 1. N.m.r. spectrum of α -carboline.

⁴⁵⁹ R. P. Haycock, P. B. Sheth, and W. J. Mader, *J. Am. Pharm. Assoc.* **48**, 479 (1959); *Chem. Abstr.* **53**, 20700 (1959).

⁴⁶⁰ D. Bertrand, *Bull. Soc. Chim. France* **12**, 1029 (1945).

⁴⁶¹ K. Biemann, *Tetrahedron Letters* **9** (1960); *J. Am. Chem. Soc.* **83**, 4801 (1961).

^{461a} T. G. Spitella and M. Spitella-Friedmann, *Tetrahedron Letters* **147** (1963).

⁴⁶² L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *J. Am. Chem. Soc.* **84**, 2161 (1962).

⁴⁶³ E. Clayton, R. I. Reed, and J. M. Wilson, *Tetrahedron* **18**, 1449 (1962).

⁴⁶⁴ M. Plat, D. D. Mann, J. Le Men, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. France* **1082** (1962).

The spectra of α - (Fig. 1), β - (Fig. 2), and δ -carboline (Fig. 3) have been measured using a Varian A-60 instrument.^{464a, 464b} Unfortunately, a sample of the γ -isomer was not available at this time. Due to

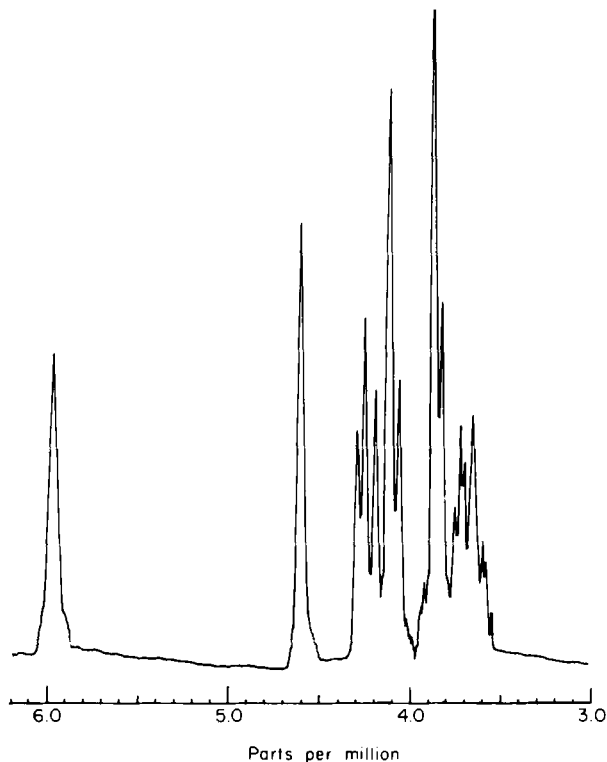


FIG. 2. N.m.r. spectrum of β -carboline.

the insolubility of the compounds in the common solvents, dimethyl sulfoxide was employed, a solvent band at 7.5τ being used as internal standard.

A complete analysis of the spectra is beyond the scope of this review, however a few points and tentative suggestions are worth making. The band at 719 cps towards low field in the spectrum of β -carboline is due to the *ind*-N-H group. The single proton singlet at 555 cps is

^{464a} We are grateful to Dr. R. G. Micetich for these determinations. Chemical shifts are quoted in cps to low field of $\tau = 10.0$ (60 M/c).

^{464b} R. A. Abramovitch and I. D. Spenser, *Can. J. Chem.* in press (1964).

undoubtedly due to C_1-H and the doublet centred at 515 cps ($J_{3,4}$ 6 cps) to C_3-H . The bands for C_4-H (a pyridine β -proton) overlap with those of the phenyl protons at higher field. The corresponding assignments for δ -carboline appear to be quite straightforward. The *ind*-N-H proton gives rise to a band at 704 cps. A single-proton doublet ($J_{2,3}$ 4 cps) centred at 520 cps may be attributed to C_2-H (pyridine α -proton). At much higher resolution this may be seen to be

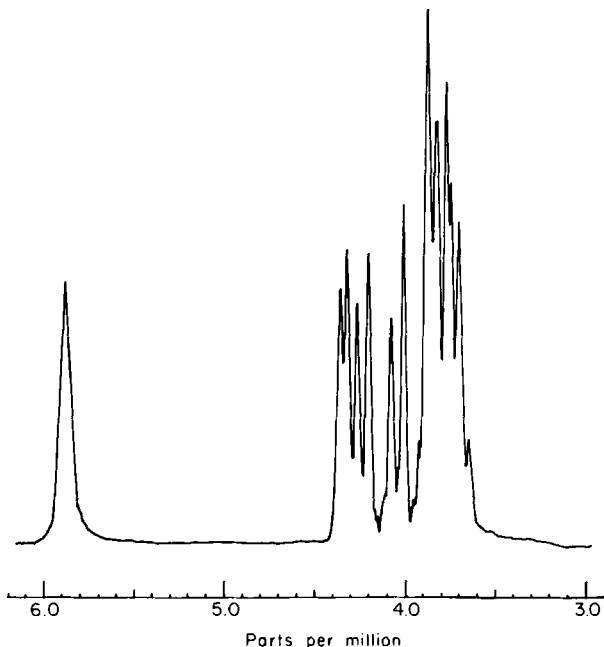


FIG. 3. N.m.r. spectrum of δ -carboline.

a quartet ($J_{2,4}$ 1 cps), as expected. A second single-proton doublet ($J_{3,4}$ 8 cps), centred at 506 cps, is probably due to C_4-H (pyridine γ -proton). The single-proton doublet (J 8 cps) at 480 cps may be due to C_3-H , but this seems to be a somewhat low field for a pyridine β -proton absorption (though lines within the range 479–499 cps have been attributed to pyridine β -protons⁴⁶⁵) and one would have expected the resonance due to this proton to give rise to a quartet. It is more

⁴⁶⁵ E. J. Poziomek, D. N. Kramer, W. A. Mosher, and H. O. Michel, *J. Am. Chem. Soc.* **83**, 3616 (1961).

likely that this doublet is due to C_8-H (cf. the lines due to C_8-H in quinoline⁴⁶⁷) and that the lines for C_3-H overlap with those of the phenyl protons. It is of interest to note that, if the above assignments are correct, the band corresponding to C_1-H in β -carboline is at a much lower field than that for C_3-H in β -carboline and that for C_2-H in δ -carboline, and is certainly at a lower field than that at which one would usually expect to find a pyridine α -proton.⁴⁶⁶ A similar situation is observed in isoquinoline.⁴⁶⁷ The electron-attracting character of the *ind-N* may also play a role here. An analogous effect appears to be in operation in δ -carboline, where C_4-H (corresponding to H_γ in pyridine) absorbs at a lower field than expected.

The interpretation of the α -carboline spectrum is more complicated and only tentative suggestions can be made at this time. The *ind-N-H* absorbs quite unexceptionally at 723 cps. Two bands appear at 519 and 511 cps respectively, each one having an area corresponding to one proton. A single-proton doublet (J 7 cps) is centered at 496 cps. One of the bands at 519 and 511 cps is undoubtedly due to C_2-H , and it is then tempting to suggest that these peaks are caused by overlapping doublets due to C_2-H and C_4-H ($J_{2,3} \sim J_{3,4} \sim 7$ cps). C_3-H would be expected to give rise to a quartet due to coupling with two non-equivalent protons, so that the doublet at 496 cps may be due to C_8-H . No firm assignment can be made without further studies.

⁴⁶⁶ R. A. Abramovitch, Giam Choo-Seng, and A. D. Notation, *Can. J. Chem.* **38**, 761 (1960); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry." Pergamon Press, New York, 1959.

⁴⁶⁷ J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," p. 268. McGraw-Hill, New York, 1959.

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Applications of the Hammett Equation to Heterocyclic Compounds*

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I. Introduction

A. GENERAL

Ever since its original formulation,¹ the Hammett equation has been one of the most widely discussed and applied relations between structure and reactivity of organic compounds, and it has been

*This work was supported in part by a grant from the Petroleum Research Fund, administered by the American Chemical Society; this support is gratefully acknowledged.

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¹ L. P. Hammett, *J. Am. Chem. Soc.* **59**, 96 (1937); *Trans. Faraday Soc.* **34**, 156 (1938).

reviewed repeatedly.²⁻⁵ This equation relates the relative reactivities of series of di- and poly-substituted benzene derivatives through Eq. (1), where k^0 is the rate of some reaction occurring at the substituent (hereafter to be called the side-chain) in a monosubstituted benzene, and k is the rate of the corresponding reaction of a compound carrying an additional substituent in the *meta* or *para* position relative to the side-chain. σ is a *substituent constant*, presumably dependent *only* on the nature and position of the second substituent,

$$\log(k/k^0) = \sigma\rho \quad (1)$$

and ρ is a *reaction constant* dependent only on the nature of the side-chain, the reaction, and the conditions under which the reaction occurs. If the reaction is an equilibrium process, k and k^0 may be equilibrium constants, and they may also represent certain physical properties.

Since one of the present authors reviewed this relation a decade ago,³ work has continued along several rather divergent lines. Since many of these developments are only of marginal interest in connection with the present discussion, we will restrict ourselves to the briefest mention of many of these.

1. Theoretical Work

Following the early work by one of the authors⁶ and by Sixma⁷ on the evaluation of substituent and reaction constants by molecular orbital theory, little more has been done along these lines. Reaction constants have further been treated theoretically^{8,9} with at least moderate success, and a complete theoretical treatment of the Hammett equation¹⁰ awaits detailed testing.

² L. P. Hammett, "Physical Organic Chemistry," Chapter VII. McGraw-Hill, New York, 1940.

³ H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).

⁴ R. W. Taft, Jr., in "Steric Effects in Organic Chemistry" (M. Newman, ed.) Chapter 13. Wiley, New York, 1956.

⁵ J. Hine, "Physical Organic Chemistry," 2nd Edn., Chapter IV., McGraw-Hill, New York, 1962.

⁶ H. H. Jaffé, *J. Chem. Phys.* **20**, 279, 778, 1554 (1952); **21**, 415 (1953); *J. Am. Chem. Soc.* **76**, 5843 (1954); **77**, 274 (1955).

⁷ F. L. J. Sixma, *Rec. Trav. Chim.* **72**, 673 (1953).

⁸ M. Charton, Abstr. of Papers, 137th Meeting, Am. Chem. Soc., Cleveland, Ohio, April 1960, p. 92 O.

⁹ J. L. Roberts and H. H. Jaffé, *Tetrahedron* **19**, Suppl. 2, 455 (1963).

¹⁰ C. Guérillot, *J. Chim. Phys.* **57**, 1039 (1960); **59**, 109 (1962).

Hammett originally demonstrated that the *sigma-rho* relation might be expected to hold if entropies of activation (or entropy changes) were constant in a series.² It has since been shown that a sufficient condition is a linear relation between enthalpies and entropies of activation (or reaction),³ and such linear relations are frequently encountered.¹¹ Although the existence of such linear relations has always appeared somewhat mysterious, some rationale for this relationship has recently been given.¹²

2. Extensions

Probably the most important development of the past decade was the introduction by Brown and co-workers¹³ of a set of substituent constants,¹⁴ σ^+ , derived from the solvolysis of cumyl chlorides and presumably applicable to reaction series in which a delocalization of a positive charge from the reaction site into the aromatic nucleus is important in the transition state or, in other words, where the importance of resonance structures placing a *positive* charge on the substituent (+*M* effect) changes substantially between the initial and transition (or final) states. These σ^+ -values have found wide application, not only in the particular side-chain reactions for which they were designed, but equally in electrophilic nuclear substitution reactions. Although such a scale was first proposed by Pearson *et al.*¹⁵ under the label of σ_e , and by Deno *et al.*,¹⁶ Brown's systematic work made the scale definitive.

A complete re-evaluation of σ -values by statistical methods, as demanded in 1953,³ has been attempted by one of the present authors by a cumbersome iterative procedure. This work was abandoned, however, when it was found that the resulting values were extremely sensitive to minor changes in the data used. Consequently, the carefully selected normal values of McDaniel and Brown,¹⁷ derived from

¹¹ J. E. Leffler, *J. Org. Chem.* **20**, 1202 (1955).

¹² J. E. Leffler and E. Grunwald "Rates and Equilibria of Organic Reactions," Chapter 9. Wiley, New York, 1963.

¹³ H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.* **79**, 1913 (1957); **80**, 4979 (1958); Y. Okamoto and H. C. Brown, *J. Org. Chem.* **22**, 485 (1957).

¹⁴ By agreement between the workers who have introduced these terms, σ -values are now generally called σ , σ^- , and σ^+ for the values applicable to normal reactions and to reactions calling strongly for $-M$ and $+M$ effects, respectively.

¹⁵ D. E. Pearson, J. F. Baxter, and J. C. Martin, *J. Org. Chem.* **17**, 1511 (1952).

¹⁶ N. C. Deno and A. Schriesheim, *J. Am. Chem. Soc.* **77**, 3051 (1955); N. C. Deno and W. L. Evans, *ibid.* **79**, 5804 (1957).

¹⁷ D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

thermodynamic acid dissociation constants of benzoic acids, must be considered as the best available σ -values.

The use of the Hammett equation has also been extended to several new types of applications. Since these are not germane to the subject matter of the present chapter, we will simply mention work on applications to ethylenic and acetylenic compounds¹⁸; the various applications to physical properties, such as infrared frequencies and intensities,¹⁹ ultraviolet spectra,²⁰ polarographic half-wave potentials,²¹ dipole moments,²² NMR²³ and NQR spectra,²⁴ and solubility data²⁵; and applications to preparative data²⁶ and biological activity.²⁷

3. Detailed Examination of the Hammett Equation

In addition to the above general extensions of the Hammett equation in the sense in which it was originally conceived, there have been a number of attempts to refine the equation and extract more detailed information from it, or provide more general justification for it.

Two groups of workers^{28, 29} have demonstrated conclusively that the concept of three sets of substituent constants,¹⁴ σ , σ^- , and σ^+ , is inadequate and that actually substantially continuous ranges of such constants are necessary for practically all *para* substituents, as well as for certain substituents in the *meta* position. Although their arguments, as well as their data and conclusions, are unassailable, it remains surprising that the naïve approach using three selected sets is so useful and successful; during the past decade we have seen and examined

¹⁸ M. Charton and H. Meislich, *J. Am. Chem. Soc.* **80**, 5940 (1958); M. Charton, *J. Org. Chem.* **26**, 735 (1961).

¹⁹ C. N. R. Rao and R. Venkataraghavan, *Can. J. Chem.* **39**, 1757 (1961); T. L. Brown, *Chem. Rev.* **58**, 581 (1958).

²⁰ See H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Section 12.25, p. 256. Wiley, New York, 1962.

²¹ P. Zuman, *Collection Czech. Chem. Commun.* **25**, 3225 (1960).

²² L. K. H. Van Beek, *Rec. Trav. Chim.* **76**, 729 (1957); O. Exner, *Collection Czech. Chem. Commun.* **25**, 643 (1960).

²³ R. W. Taft, Jr., *J. Am. Chem. Soc.* **79**, 1045 (1957).

²⁴ See, e.g., H. O. Hooper and P. J. Bray, *J. Chem. Phys.* **33**, 334 (1960).

²⁵ M. Rapoport, C. K. Hancock, and E. A. Meyers, *J. Phys. Chem.* **66**, 1752 (1962).

²⁶ O. Exner, *Collection Czech. Chem. Commun.* **26**, 1 (1961).

²⁷ O. R. Hansen, *Acta Chem. Scand.* **16**, 1593 (1962).

²⁸ H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.* **78**, 815 (1959).

²⁹ R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.* **81**, 5343 (1959); R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *ibid.* **81**, 5352 (1959).

several hundred reaction series which were excellently correlated by just the three sets. In our opinion, one is justified to continue to use the *standard* Hammett equation for general purpose work, for all recognition of trends, for rough predictive purposes, and for mechanistic classification. Only when fine details are under discussion or intimate structures of transition states under consideration, and when a large amount of experimental material has been collected, does it appear necessary to proceed to the more refined treatments suggested by Wepster's and by Taft's work. Such refinements then undoubtedly permit a more detailed interpretation of the experimental material and a more intimate recognition of the nature of reactions. Availability of these refined techniques, however, does not invalidate the more naïve approach, which, in most cases, ought to be the *first* step in the evaluation of experimental data.

A more quantitative formulation of the varying resonance effects in electrophilic nuclear substitution reactions has been suggested by Tsuno,³⁰ who has proposed to use Eq. (2), where $\Delta\sigma^+$ is a resonance exaltation term, and r is a susceptibility constant.

$$\log(k/k^0) = \sigma\rho(1 + r\Delta\sigma^+) \quad (2)$$

Similar, although less well documented, is Bryson's observation³¹ that a constant term must occasionally be included in the Hammett equation, i.e. $\Delta pK = \sigma\rho + a$, which means that the intercept is significantly different from the equilibrium constant for the parent compound.

A completely different approach has been taken by Hine,^{5, 32} who has considered that the substituent and reaction center are not really distinct, both being substituents in a benzene nucleus, and has then related substituent and reaction constants. Although of considerable theoretical interest, Hine's work has little bearing on practical applications of the Hammett equation since he starts from the premise of *unique, single-valued* substituent constants. This premise is invalid whether we are utilizing the naïve approach with three separate, well-defined sets or the more refined methods with a continuous range of *para* values.

A detailed examination of substituent constants, finally, has enabled

³⁰ Y. Tsuno, *Mem. Inst. Sci. Ind. Res., Osaka Univ.* **16**, 197 (1959); see also Y. Tsuno, T. Ibata, and Y. Yukawa, *Bull. Chem. Soc. Japan* **32**, 960 (1959); Y. Yukawa and Y. Tsuno, *ibid.* **32**, 965, 971 (1959).

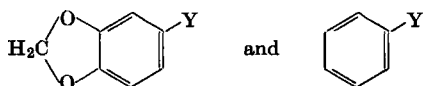
³¹ A. Bryson and R. W. Mathews, *Australian J. Chem.* **16**, 401 (1963).

³² J. Hine, *J. Am. Chem. Soc.* **81**, 1126 (1959).

Taft's group^{4, 33} to arrive at a (at least *pro forma*) separation of resonance and inductive effects.

B. APPLICATIONS TO REACTIONS OF HETEROCYCLIC COMPOUNDS

The first application of the Hammett equation to a heterocyclic system is contained in Hammett's original work,^{1, 2} where his "reaction series 9" is the ionization of 5-substituted 2-furoic acids.³⁴ In addition, one of Hammett's original substituents is the CH_2O_2 -group, i.e., the σ -value which compares the reactivity of



where Y is the reacting side-chain. A decade ago, very few additional applications were available; these included the basicities of 5-*N*-phenylaminotetrazanes,³⁵ the equilibria between the *N*-phenyl- and 1-phenyl-5-aminotetrazanes, and the hydrolyses of substituted phthalides,³⁶ aside from substituent constants for aza substitution.³⁷ Since that time a larger number of such applications has appeared in the literature; some of these were collected in a summary by Otsuji and Imoto.³⁸

It is the purpose of the present review to examine in what ways the Hammett equation can be applied to heterocyclic systems, to give examples of such applications, and to examine the special problems which arise in the process. In view of the tremendous difficulties involved in systematically searching the literature for the type of data required, no attempt will be made at an exhaustive coverage of all available information. The different possible applications will be discussed and, where feasible, illustrated. If an unjustified number of such illustrations are taken from the authors' work, this should be

³³ R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.* **80**, 2436 (1958); R. W. Taft, Jr., *J. Phys. Chem.* **64**, 1805 (1960); see also J. L. Roberts and H. H. Jaffé, *J. Am. Chem. Soc.* **81**, 1635 (1959).

³⁴ W. E. Catlin, *Iowa State Coll. J. Sci.* **10**, 65 (1935).

³⁵ R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.* **76**, 88 (1954); **77**, 2264 (1955).

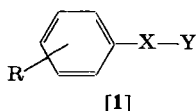
³⁶ A. Tasman, *Rec. Trav. Chim.* **46**, 653 (1927).

³⁷ Ref. 3, p. 245, Table 18; see also H. H. Jaffé, *J. Chem. Phys.* **20**, 1554 (1952).

³⁸ Y. Otsuji and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1297 (1959); *Bull. Osaka Prefect. Univ.* **6A**, 115 (1958).

considered as a matter of convenience rather than as an inflated evaluation of their worth. As an arbitrary limitation, reactions in which a series of substituted substrates react with a constant heterocyclic reagent will be completely ignored, since here the substituent effects and the heterocyclic reagent are more or less in a trivial relationship. Similarly, and for the same reasons, reactions in which a benzene ring is attached to a reacting heterocyclic group will generally be ignored.

Although the application of the Hammett equation to side-chain reactions of disubstituted benzene derivatives (**1**) is relatively straightforward, the introduction of a heteroatom somewhere in the aromatic



system leads to a considerable multiplication of possibilities which need to be considered. In **1**, R will be considered as the *substituent*, Y the *reaction center*, and X any connection between Y and the benzene nucleus; X may be, and often is, missing.

The following are the particular situations arising in heterocyclic aromatic chemistry which can be, and have been, treated in terms of the Hammett equation and which will be discussed in the following sections.

(1) Replacement of a $\geq\text{CH}$ or $-\text{CH}=\text{CH}-$ group in the aromatic ring by a heteroatom.

(2) Reactivity of a heteroatom, as affected by other substituents.

(3) Reactivity of groups attached to a heteroatom.

(4) Transmission through a heterocyclic ring, both six- and five-membered. Due to the reduced symmetry of the ring, in general, two *para* and several *meta* relations between substituent and side-chain exist.

(5) Fused ring systems. Here, the above situations (cf. 1-4) are repeated and some new cases arise.

II. Substituent Constants for Heteroatoms

A. SIX-MEMBERED RINGS

The concept that replacement of a $\geq\text{CH}$ group in benzene by a heteroatom can be treated as a substitution in the sense of the

Hammett equation and that σ -values can be assigned to such "substituents" was introduced some ten years ago³⁷ but seems to have found relatively little acceptance. Since such substitution is likely to exert at best only a minor steric effect, even substitution *alpha* to the reacting side-chain was treated in this manner, at least *pro forma*. Unfortunately, at the time, the experimental material for a critical evaluation was lacking, and the situation has not greatly improved in the intervening decade. There are undoubtedly many factors which contribute to the relative scarcity of experimental data, among which the relatively large difference in reactivity between heterocycles and benzene derivatives and the special reactions occurring at the heteroatom are probably important; however, possibly the most significant factor arises from the facts that chemists do not consider a heteroatom as a "substituent" and that the workers interested in substituted benzenes tend to ignore heterocycles as modified benzenes, while investigators concerned with heterocycles tend to compare their substrate with an unsubstituted benzene, but only rarely with an entire series of substituted derivatives.

The only substitution for which at all extensive data are available is the replacement of $\geq\text{CH}$ by $\geq\text{N}$, the aza substitution. Since steric effects are likely to be relatively unimportant in α -substituted pyridines, there is some hope of treating the α - $\geq\text{N}$ group in the framework of the Hammett equation on the same basis as the β - and γ -analogs. Some initial data for this group were given in a previous review.³ These data were extended and critically discussed by Favini and Simonetta,³⁹ who did not find good agreement with either theoretical or previous empirical values in the alkaline hydrolysis of the three pyridine-carboxylic esters, but found excellent agreement with the previous values in the alkaline hydrolysis of the amides. Using these σ -values to delimit LCAO parameters, Favini and Carrà⁴⁰ arrived at a MO treatment of pyridine in excellent agreement with experimental findings in regard to the dipole moment and bond distances. Willi and Meier⁴¹ found good agreement of the pK values of 2-benzenesulfonamidopyrimidine with values predicted on the basis of published σ -values³⁷ but very poor agreement for the 2-benzenesulfonamido-

³⁹ M. Simonetta and G. Favini, *Gazz. Chim. Ital.* **84**, 566 (1954); **85**, 1026 (1955); G. Favini, *Rend. Ist. Lombardo Sci. Lettere Pt. I* **91**, 162 (1957).

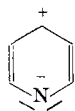
⁴⁰ G. Favini and S. Carrà, *Gazz. Chim. Ital.* **87**, 1367 (1957).

⁴¹ A. V. Willi and W. Meier, *Helv. Chim. Acta* **39**, 54 (1956); cf. A. V. Willi, *ibid.* **39**, 46 (1956).

pyridine. They ascribe the failure to obtain a good prediction in this case to a tautomeric equilibrium.

The problem has also been considered by Bray and co-workers,⁴² using nuclear quadrupole coupling data, which they had previously shown to be related to σ -values²⁴; they found good agreement for the β -position of aza substitution but rather wide divergence from other values, both theoretical and experimental, for the γ -position. Shindo⁴³ has treated the effect of the $\geq N$ group on the carbonyl, N—O, and C \equiv N stretching frequencies of acetyl-, ethoxycarbonyl-, nitro-, and cyano-pyridines in terms of the Hammett equation with fair success using $\sigma_\alpha = 1.02$, $\sigma_\beta = 0.62$ and $\sigma_\gamma = 0.93$, in fair agreement with other available values.

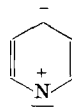
The total experimental material known to the present authors is summarized in Table I. Unfortunately, few of the data presented come from the most thoroughly studied and best documented reaction series. However, the picture is quite discouraging. Very likely, separate σ^- - and normal σ -values and, possibly further, a separate σ^+ -value might be applicable for the 2- and 4-aza groupings since resonance structures such as **2-4** may contribute in appropriate systems, although **4** may not be too important, and, consequently,



[2]



[3]



[4]

σ^- -values may not differ too widely from σ -values. Since the charges in **2** and **4** actually reside in the ring, the pyridine system may, in addition, be particularly subject to the variability of σ -values, and consequently a careful analysis of some rather extensive material in the sense of some of the most refined methods^{28, 29, 33} might be very profitable before the use of σ -values for aza substitution can be abandoned.

It has also been suggested to treat various modified heterocyclic nitrogen atoms in the same manner. Thus, σ -values have been proposed for the protonated aza nitrogen, $\geq N^+H$,⁴⁴ and for the $\geq N^+O^-$

⁴² P. J. Bray, S. Moskowitz, H. O. Hooper, R. G. Barnes, and S. Siegel, *J. Chem. Phys.* **28**, 99 (1958); H. O. Hooper and P. J. Bray, *ibid.* **30**, 957 (1959).

⁴³ H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **5**, 472 (1957).

⁴⁴ H. H. Jaffé, *J. Am. Chem. Soc.* **77**, 4445 (1955).

TABLE I
SUBSTITUENT CONSTANTS FOR AZA- AND MODIFIED AZA-SUBSTITUENTS

Substituent	α	β	γ	Type ^a	Solvent	Reaction ^b	References
>N	0.45	0.62	0.67	σ	H ₂ O	p <i>K</i> of pyridines	<i>c</i>
	0.81	0.62	0.93	σ	87.83% EtOH	basic hydrolysis of ethyl benzoates	<i>d</i>
	1.1	1.3	1.6	σ	88% dioxane	basic hydrolysis of ethyl benzoates	<i>e, f</i>
	0.37	0.55	0.95	σ	60% EtOH	basic hydrolysis of benzamides	<i>e, f</i>
	0.92	0.10	—	σ	vapor phase	ArCl + Na \rightarrow Ar ⁺	<i>g</i>
	—	0.34	0.99	σ	CHCl ₃	infrared absorption intensities of C \equiv N frequency in benzonitriles	<i>h</i>
	0.38	—	—	σ	80 wt-% methyl cellosolve	p <i>K</i> of benzenesulfonamides ⁱ	<i>j</i>
	0.34	—	—	—	—	—	—
	0.38	—	—	—	—	—	—
	—	0.27 ^t	—	σ	no solvent	N.Q.R. frequencies of bromobenzenes	<i>k</i>
	—	0.40	—0.08 <i>or</i>	σ	no solvent	N.Q.R. frequencies of chlorobenzenes	<i>k</i>
	—	0.38 ^t	0.20 ^t	—	—	—	—
	1.02	0.62	0.93	σ	CS ₂	side-chain stretching frequency of acetyl-, nitro-, ethoxycarbonyl-, and cyano-substituted benzenes (averages of four values)	<i>m</i>
	0.40	—	—	σ^-	no solvent	Copolymerization of styrenes with styrene	<i>n</i>
	0.41	—	—	σ^-	80 wt-% methyl cellosolve	p <i>K</i> of benzenesulfanilides (PhSO ₂ NHAr)	<i>o</i>
	—	0.74	0.86	$\sigma^+(?)$	the substituted toluene	hydrogen atom abstraction from toluenes with <i>t</i> -butoxy radical	<i>p</i>
	0.58	0.76	1.26	σ^-	butyl carbitol	Wolff-Kishner reduction	<i>t</i>

$\geq\text{NH}^+$	—	2.07	1.97	σ	H ₂ O	pK of pyridines	c
	—	2.1	2.3	σ	H ₂ O	pK of benzoic acids	q
	—	2.1	4.0	σ^-	H ₂ O	pK of anilines	q
$\geq\text{N}^+-\text{O}^-$	—	1.48	1.35	σ	H ₂ O	pK of benzoic acids	r
	—	1.18	0.23	σ^+	CS ₂	carbonyl stretching frequency in acetophenones	s
$\geq\text{N}^+-\text{OH}$	—	1.59	1.88	σ^-	H ₂ O	pK of phenols	r
	—	2.3	3.9	σ^-	H ₂ O	pK of anilines	q

^a Indicates the type of σ -value (σ^+ , σ or σ^-) used in the reaction series from which the ρ -value needed was obtained.

^b The reaction series in which the $\geq\text{N}$ group is treated as a substituent.

^c σ_a , T. Nakayima and A. Pullman, *J. Chim. Phys.* **55**, 793 (1958); σ_B , D. J. Brown, "The Pyrimidines," Chapter 13. Interscience, New York, 1962; σ_Y , A. Shin-Chuen and R. F. Trimble, *J. Phys. Chem.* **65** 863 (1961).

^d H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).

^e M. Simonetta and G. Favini, *Gazz. Chim. Ital.* **84**, 566 (1954); **85**, 1026 (1955).

^f G. Favini, *Rend. Inst. Lombardo Sci. Lettere* Pt. I **91**, 162 (1957).

^g F. Riding, J. Scanlon, and E. Warhurst, *Trans. Faraday Soc.* **52**, 1354 (1956).

^h P. Sensi and G. G. Gallo, *Gazz. Chim. Ital.* **85**, 235 (1955).

ⁱ From compounds with several "substituents," assuming additivity of substituent constants.

^j W. Simon, G. H. Lyssy, A. Moriköfer, and E. Heilbronner, "Zusammenstellung von Scheinbaren Dissoziations Konstanten." Juris Verlag, Zürich, 1959.

^k P. J. Bray, S. Moskowitz, H. O. Hooper, R. G. Barnes, and S. Siegel, *J. Chem. Phys.* **28**, 99 (1958); H. O. Hooper and P. J. Bray, *ibid.* **30**, 957 (1959).

^l Two different Cl³⁵ resonance frequencies were given for the same compound.

^m H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **5**, 472 (1957).

ⁿ C. Walling, E. R. Briggs, and K. B. Wolfstirn, *J. Am. Chem. Soc.* **70**, 1543 (1948); C. Walling, E. R. Briggs, K. B. Wolfstirn, and F. R. Mayo, *ibid.* 1537 (1948).

^o W. Simon, A. Moriköfer, and E. Heilbronner, *Helv. Chim. Acta* **40**, 1918 (1957).

^p K. M. Johnston and G. W. Williams, *Chem. Ind. (London)* 328 (1958).

^q H. H. Jaffé, *J. Am. Chem. Soc.* **77**, 4445 (1955).

^r H. H. Jaffé, *J. Am. Chem. Soc.* **76**, 3527 (1954).

^s H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **6**, 117 (1958).

^t H. H. Szmant and C. M. Harmuth, *J. Am. Chem. Soc.*, in press.

group in pyridine oxide⁴⁵ and its protonated analog $\geq\text{N}^+\text{OH}$.⁴⁴ The available experimental data in all three cases are insufficient to demonstrate whether these values have any general applicability. For $\geq\text{N}^+\text{O}^-$, however, there can be little doubt that separate σ^- , σ^- , and σ^+ -values must be needed, since in the correlation of the basicities of substituted pyridine oxides, 4-substituents required either σ^+ - or σ^- -values according to the sign of their M effect.⁴⁶ Actually, Shindo⁴⁷ has used the infrared spectra of 3- and 4-acetyl-, -ethoxycarbonyl-, -nitro-, and -cyano-pyridine 1-oxides to calculate a σ_p -value of 0.25 and a σ_m -value of 1.18 for $\geq\text{N}^+\text{O}^-$, roughly equal for all four series. The *para* value most likely should be considered as a σ^+ -value; the σ_m -value is somewhat smaller than the above values, but of the same order of magnitude. Here again, a detailed investigation might be very revealing.

B. FIVE-MEMBERED RINGS

The chemical and particularly the physical similarity between thiophene and benzene has intrigued chemists for a long time, and comparison between phenyl and thienyl derivatives has often been made. Accordingly, it seems somewhat surprising that the effect of replacement of a "vinyl" group, $-\text{CH}=\text{CH}-$, in benzene by $>\text{S}$ has never been considered as tractable in terms of a σ -value and the Hammett equation. Unfortunately, again, experimental data seem to be scarce, and most of those available to use at the present come from rather old work in which the Hammett equation has not been too successful. What little data are available and are summarized in Table II, however, raise serious doubt whether this approach may be fruitful. Similar data for oxa, aza, and seleno derivatives of cyclopentadiene are also included in Table II.

C. HETEROCYCLIC SUBSTITUENTS

In view of the extremely wide variety of groups which occur as substituents in benzene derivatives and for which substituent constants have been calculated, it is surprising that almost none of them

⁴⁵ H. H. Jaffé, *J. Am. Chem. Soc.* **76**, 3527 (1954).

⁴⁶ H. H. Jaffé, *J. Org. Chem.* **23**, 1790 (1958).

⁴⁷ H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **6**, 117 (1958).

TABLE II
SUBSTITUENT CONSTANTS FOR HETEROATOMS IN FIVE-MEMBERED RINGS



Substituent	α	β	Type ^a	Solvent	Reaction ^b	References
	0.61	—	σ	78% EtOH	p <i>K</i> of benzoic acids	<i>c</i>
	1.08	0.25	σ	H ₂ O	p <i>K</i> of benzoic acids	<i>d, e</i>
	0.24	—	σ	85% EtOH	basic hydrolysis of ethyl benzoates	<i>f</i>
	0.28	—	σ	87.83 wt-% EtOH	basic hydrolysis of ethyl benzoates	<i>g</i>
	0.29	—	σ	70% dioxane	basic hydrolysis of ethyl benzoates	<i>c</i>
	0.70	—	σ	92.5% EtOH	basic hydrolysis of benzalchlorimines	<i>h</i>
	0.66	—	σ	CCl ₄	N.M.R. frequencies of benzaldehydes	<i>i</i>
	-0.15	—	σ	H ₂ O	p <i>K</i> of benzal oximes	<i>j</i>
	-0.37	—	σ^+	60% dioxane	ArCH(OH)CH=CHMe $\xrightarrow{H^+}$ ArCH=CHCH(OH)Me	<i>k</i>
	-0.98	—	σ^+	MeOH:aq. HClO ₄ (5:2)	protodesilylation of trimethylsilylbenzenes	<i>l</i>
	0.36	—	σ	78% EtOH	p <i>K</i> of benzoic acids	<i>c</i>
	0.71	0.12	σ	H ₂ O	p <i>K</i> of benzoic acids	<i>d, e</i>
	-0.03	—	σ	87.83 wt-% EtOH	basic hydrolysis of ethyl benzoates	<i>g</i>
	0.05	-0.004	σ	85% EtOH	basic hydrolysis of ethyl benzoates	<i>f</i>
	0.005	-0.005	σ	70% dioxane	basic hydrolysis of ethyl benzoates	<i>c</i>
	-0.27	—	σ^+	60% dioxane	ArCH(OH)CH=CHMe $\xrightarrow{H^+}$ ArCH=CHCH(OH)Me	<i>k</i>

Table II continued on p. 222

TABLE II—continued

Substituent	α	β	Type ^a	Solvent	Reaction ^b	References
>S	-0.85	—	σ^+	MeOH:aq. HClO ₄ (5:2)	protodesilylation of trimethylsilylbenzenes	<i>l</i>
	-0.80	-0.45	σ^+	H ₂ SO ₄ /HOAc	protodesilylation of trimethylsilylbenzenes	<i>m</i>
	0.58	—	σ^-	butyl carbitol	Wolff-Kishner reduction	<i>o</i>
>Se	0.28	—	σ	80% EtOH	p <i>K</i> of benzoic acids	<i>g</i>
>N—H	-0.25	—	σ	H ₂ O	p <i>K</i> of benzoic acids	<i>d</i>

^a Indicates the type of σ -value (σ^+ , σ , or σ^-) used in the reaction series from which the ρ -value needed was obtained.

^b The reaction series in which the \geq N group is treated as a substituent.

^c S. Oae and C. C. Price, *J. Am. Chem. Soc.* **79**, 2547 (1957).

^d A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Table 8.2, p. 127. Wiley, New York, 1962.

^e W. E. Catlin, *Iowa State Coll. J. Sci.* **10**, 65 (1955).

^f G. Costa and P. Blasina, *Z. Physik. Chem. (Frankfurt)* **4**, 24 (1955).

^g K. Kindler, *Ber.* **69B**, 2792 (1936).

^h C. R. Hauser, J. W. LeMaistre, and A. E. Rainsford, *J. Am. Chem. Soc.* **57**, 1056 (1935).

ⁱ The N.M.R. spectrum of furfural was reported by E. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glazier, *J. Am. Chem. Soc.* **80**, 1204 (1958); σ was obtained from the data for benzaldehydes reported by R. E. Klink and J. B. Stothers, *Can. J. Chem.* **40**, 1071 (1962).

^j D. L. Brady and R. F. Goldstein, *J. Chem. Soc.* 1918 (1926).

^k E. A. Braude and J. S. Fawcett, *J. Chem. Soc.* 4158 (1952).

^l C. Eaborn and J. A. Sperry, *J. Chem. Soc.* 4921 (1961).

^m E. B. Deans and C. Eaborn, *J. Chem. Soc.* 2303 (1959).

ⁿ Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **28**, 2164 (1958); *Chem. Abstr.* **53**, 2245 (1959).

^o H. H. Szmant and C. M. Harmuth, *J. Am. Chem. Soc.*, in press.

are heterocyclic. Hammett's original tabulation included the 3,4-methylenedioxy group, 3,4-CH₂O₂, with a σ -value of -0.159 . The few other such values which have become available are listed in Table III.

TABLE III
SUBSTITUENT CONSTANTS FOR HETEROCYCLIC SUBSTITUENTS

Substituent	σ	Type ^a	Solvent	Reaction ^b	Reference
3,4-CH ₂ O ₂	-0.159	σ	H ₂ O	p <i>K</i> of benzoic acids	<i>c</i>
4-(CH ₂) ₅ N	-0.117	σ	50% EtOH	p <i>K</i> of <i>p</i> -phenyl-N-arylbenzamidines	<i>d</i>
3,4-(CH) ₃ N (6-Quinolyl)	0.23	σ	50% MeOH	p <i>K</i> of benzoic acids	<i>e</i>
3,4-N(CH) ₃ (7-Quinolyl)	0.24	σ	50% MeOH	p <i>K</i> of benzoic acids	<i>e</i>
3,4-(CH) ₃ N	0.46	σ^-	H ₂ O	p <i>K</i> of phenols	<i>f</i>
3,4-N(CH) ₃	0.47	σ^-	H ₂ O	p <i>K</i> of phenols	<i>f</i>
4-(γ -C ₅ H ₅ NH ⁺)	0.65	σ^-	H ₂ O	p <i>K</i> of anilinium ions	<i>g</i>
4-(γ -C ₅ H ₅ NO)	0.33	σ^-	H ₂ O	p <i>K</i> of anilinium ions	<i>g</i>

^a Indicates the type of σ -value (σ^+ , σ , or σ^-) used in the reaction series from which the ρ -value needed was obtained.

^b The reaction series in which the $\equiv\text{N}$ group is treated as a substituent.

^c L. P. Hammett, "Physical Organic Chemistry," Chapter VII. McGraw-Hill, New York, 1940.

^d J. Cymerman-Craig, M. J. Parker, and P. Woodhouse, *J. Chem. Soc.* 3050 (1953).

^e R. C. Elderfield and M. Siegel, *J. Am. Chem. Soc.* 73, 5622 (1951).

^f A. Albert and J. N. Phillips, *J. Chem. Soc.* 1294 (1956).

^g A. R. Katritzky and P. Simmons, *J. Chem. Soc.* 1511 (1960).

III. Reactions at the Heteroatom and at Side-Chains Attached Thereon

A. REACTIONS AT THE HETEROATOM

The only reaction series involving a reaction at a heteroatom which has been extensively studied is the basicity of substituted pyridines. The Hammett equation was first applied to this reaction simultaneously by Brown and co-workers⁴⁸ and by Jaffé and Doak.⁴⁹ A sampling

⁴⁸ H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.* 77, 1723 (1955); H. C. Brown and D. H. McDaniel, *ibid.* 77, 3752 (1955).

⁴⁹ H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.* 77, 4441 (1955).

TABLE IV
THE BASICITIES OF SUBSTITUTED PYRIDINES IN
WATER AT $\sim 25^\circ\text{C}$

Substituent	σ^a	$\Delta\text{p}K^b$	References
3-NH ₂	-0.16	0.86	<i>c</i>
3-NHAc	0.21	-0.77	<i>c</i>
3-NHCOPh	0.217	-1.43	<i>c</i>
3-OMe	0.115	-0.35	<i>c</i>
4-NH ₂	-0.66	3.94	<i>c</i>
4-NHAc	0.00	0.64	<i>c</i>
4-NHCOPh	0.078 ^d	0.09	<i>c</i>
4-OMe	-0.268	1.39	<i>c</i>
3-SMe	0.15	-0.78	<i>e</i>
4-SMe	0.00	0.74	<i>e</i>
3-F	0.337	-2.20	<i>f</i>
3-Cl	0.373	-2.33	<i>f</i>
3-Br	0.391	-2.33	<i>f</i>
3-I	0.352	-1.92	<i>f</i>
4-Cl	0.227	-1.45	<i>g</i>
3-Me	-0.069	0.51	<i>f</i>
3-Et	-0.07	0.53	<i>f</i>
3-CHMe ₂	-0.068 ^h	0.55	<i>f</i>
3-CMe ₃	-0.10	0.65	<i>f</i>
4-Me	-0.170	0.85	<i>f</i>
4-Et	-0.151	0.85	<i>f</i>
4-CHMe ₂	-0.151	0.85	<i>f</i>
4-CMe ₃	-0.197	0.82	<i>f</i>
3-Ac	0.376	-1.99	<i>i</i>
3-NO ₂	0.710	-3.42	<i>j</i>
3-OH	0.121	-0.43	<i>k</i>
3-CONH ₂	0.280	-1.72	<i>k</i>
3-CN	0.56	-3.84	<i>k</i>
3-CO ₂ ⁻	-0.1	-0.52	<i>k</i>
4-CO ₂ ⁻	0.00	-0.39	<i>k</i>
3-SO ₃ ⁻	0.05	-1.85	<i>l</i>
4-SO ₃ ⁻	0.09	-1.67	<i>l</i>

^a Substituent constants. Where possible the values were taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958). Values found elsewhere are noted.

^b The difference, $\Delta\text{p}K = \text{p}K_{\text{subst. pyridine}} - \text{p}K_{\text{pyridine}}$, where both values refer to work by the same authors determined under the same experimental conditions, is given here and is used to plot Fig. 1 and to calculate the reaction constant given in Table V to

of the existent experimental data is presented in Table IV and shown graphically in Fig. 1. It is seen that the correlation obtained is excellent,

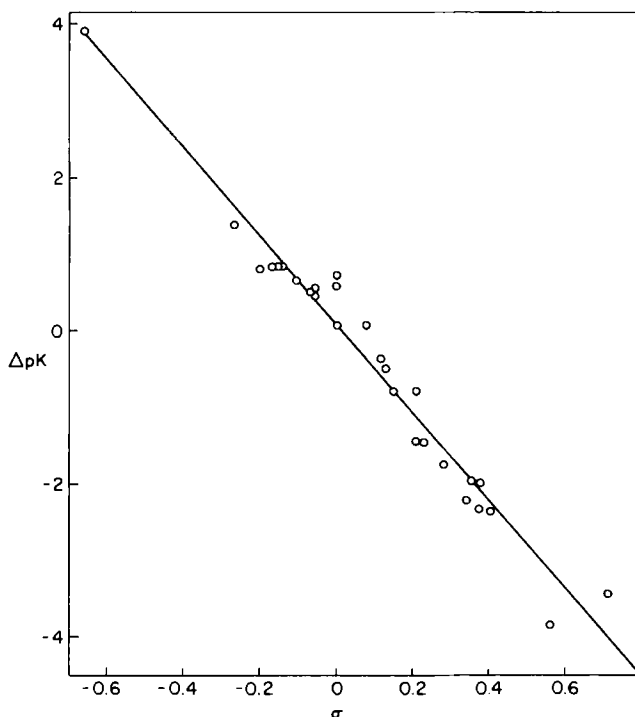


FIG. 1. The pK -values of substituted pyridines in water at approximately 25° .

minimize difficulties arising out of the different values for pK_{pyridine} obtained in different studies.

^c R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* 7317 (1959).

^d H. H. Jaffé, *Chem. Revs.* **53**, 191 (1953).

^e A. Albert and G. B. Barlin, *J. Chem. Soc.* 2384 (1959).

^f H. C. Brown and S. R. Mihm, *J. Am. Chem. Soc.* **77**, 1723 (1955); H. C. Brown and D. H. McDaniel, *ibid.* **77**, 3752 (1955).

^g A. Dondoni, G. Modena, and P. E. Todesco, *Gazz. Chim. Ital.* **91**, 613 (1961); G. Modena and P. E. Todesco, *ibid.* **90**, 1, 702 (1960).

^h From H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.* **78**, 815 (1959).

ⁱ N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.* **54**, 3469 (1932).

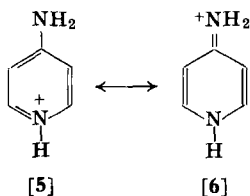
^j A. Bryson, *J. Am. Chem. Soc.* **82**, 4871 (1960).

^k H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.* **77**, 4441 (1955).

^l R. T. Evans and H. C. Brown, *J. Org. Chem.* **27**, 3127 (1962).

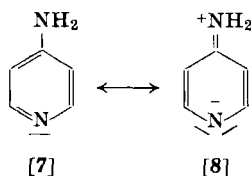
possibly, as suggested by Brown and co-workers,⁵⁰ because "the ring system is rigid and . . . the base center is not susceptible to steric inhibition of resonance phenomena." A limitation in this series is that many desirable compounds are difficult to obtain and that many others, such as the hydroxy- and mercapto-pyridines, are not capable of existence, due to the intervention of tautomeric equilibria. The Hammett equation, however, is so well obeyed by the basicities of substituted pyridines that this series is very useful in the determination of σ -values for groups for which no such values have been obtained from other sources. In addition, the large ρ -value makes the substituent constants obtained relatively certain. Such values for the $\geq N$ grouping have been included in the preceding section of this chapter. The ρ -value for this reaction series, 5.77, is of the same order of magnitude as the ρ -values for nucleophilic attack on benzene rings,³ as might have been expected since the reaction bears a formal analogy with an electrophilic substitution reaction.

It is interesting to speculate why the basicities of the substituted pyridines are well correlated by normal σ -values, rather than by σ^+ -values. Writing the resonance structures for the conjugate acid ($5 \leftrightarrow 6$)



of 4-aminopyridine, it might have been anticipated that the positive charge may be sufficiently well delocalized into the less electronegative amino-nitrogen atom to require the intervention of the σ^+ -constants. A possible interpretation is that, in the free base ($7 \leftrightarrow 8$) also, the resonance is sufficiently important that no great change in the contribution of quinoid resonance structures occurs between free base and conjugate acid; such a change appears to be the ultimate requirement for the need for the special constants (σ^+), rather than the normal ones (σ).

⁵⁰ H. C. Brown, D. H. McDaniel, and O. Häfliger, in "Determination of Organic Structures by Physical Methods" (E. A. Braude and F. C. Nachod, eds.), p. 597. Academic Press, New York, 1955.



Closely related to the basicity of pyridine is its hydrogen-bonding ability; two indices of this property have been measured for a very short series of substituted pyridines and are very well correlated by σ -values.⁵¹

Few other reactions of series of substituted pyridines have been investigated extensively. Dondoni, Modena, and Todesco⁵² have measured the rate of N-oxidation of a limited series of pyridines and found a good correlation with normal σ -values with a ρ -value of -2.23 . The N-alkylation of pyridines with alkyl iodides in nitrobenzene has been studied by Brown and Cahn⁵³ and by Clarke and Rothwell.⁵⁴ Unfortunately, the only data available are for the parent compound and for alkyl derivatives, and, since the σ -values for the various alkyl groups in a given position are substantially constant, this leaves a correlation of only three independent points. However, the rates of N-alkylation of the β - and γ -alkyl derivatives are so nearly equal that it appears as if no correlation existed. Clarke and Rothwell⁵⁴ have also studied the alkylation with allyl bromide in nitromethane at various temperatures, and in this case a more extensive series is available. The authors state that no overall Hammett correlation is obtained; however, the β -substituted derivatives fall on one straight line and the γ -derivatives on another one with a different slope. The data are shown in Fig. 2. The line for the β -compounds, $\rho = -2.53 \pm 0.31$, $r = 0.95$, is seen not to be very good; the line for the γ -derivatives, $\rho = -1.42 \pm 0.06$, $r = 0.99$, is much more satisfactory. It does not seem likely that the discrepancy is due to the intervention of resonance effects, since in this case one would expect the correlation for the γ -derivatives to be poorer than that for the β -analogs. More extensive studies with a wider variety of substituents would seem very desirable.

⁵¹ M. Tamres, S. Searles, E. M. Leighly, and D. W. Mohrman, *J. Am. Chem. Soc.* **78**, 2676 (1956).

⁵² A. Dondoni, G. Modena, and P. E. Todesco, *Gazz. Chim. Ital.* **91**, 613 (1961); G. Modena and P. E. Todesco, *ibid.* **90**, 1, 702 (1960).

⁵³ H. C. Brown and A. Cahn, *J. Am. Chem. Soc.* **77**, 1715 (1955).

⁵⁴ K. Clarke and K. Rothwell, *J. Chem. Soc.* 1885 (1960).

Chapman and co-workers⁵⁵ have investigated the nucleophilic displacement of chlorine in various chloronitropyridines by three pyridines. In each of these series of three compounds, an excellent correlation is observed, but, again, longer series would be extremely desirable. Similarly, the nucleophilic attack of a series of four pyridines on propylene oxide follows the Hammett equation with high precision.⁵⁶

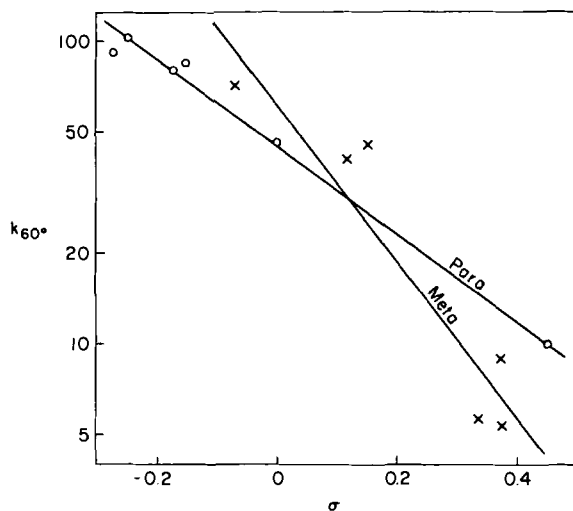


FIG. 2. A Hammett plot of the rates of alkylation of substituted pyridines with allyl bromide in nitromethane. Circles represent 4-substituted compounds and crosses 3-substituted compounds. Cf. ref. 54.

Pyridine bases are well known as ligands in complexes of transition metals, and it might well be anticipated that the equilibrium constants for the formation of such complexes, which are likely to be closely related to the base strength, would follow the Hammett equation. Surprisingly, only very few quantitative studies of such equilibria seem to have been reported, and these only for very short series of compounds. Thus, Murmann and Basolo⁵⁷ have reported the formation constants, in aqueous solution at 25°, of the silver(I) complexes

⁵⁵ E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.* 3392 (1953); R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *ibid.* 437 (1952).

⁵⁶ J. Hansen, *Svensk. Kem. Tidskr.* 67, 246, 263 (1955).

⁵⁷ R. K. Murmann and F. Basolo, *J. Am. Chem. Soc.* 77, 3484 (1955).

TABLE V
REACTION CONSTANTS FOR THE REACTIVITY OF SUBSTITUTED PYRIDINES AND PYRIDINE 1-OXIDES

Reaction ^a	Solvent	<i>T</i> ° C	ρ^a	s_ρ^b	s^c	r^d	n^e	Reference
p <i>K</i> of py	H ₂ O	~ 25	5.77 ^f	0.22	0.32	0.982	28 ^g	<i>h</i>
Py + 2-Cl-3-NO ₂ C ₅ H ₃ N → 2-RC ₅ H ₄ N ⁺ -3-NO ₂ C ₅ H ₃ N	99.8% EtOH	50	-2.78	0.37	0.05	0.991	3	<i>i</i>
	99.8% EtOH	60	-2.56	0.27	0.03	0.994	3	<i>i</i>
	99.8% EtOH	70	-2.61	0.41	0.05	0.998	3	<i>i</i>
Py + 2-Cl-5-NO ₂ C ₅ H ₃ N → 2-RC ₅ H ₄ N ⁺ -5-NO ₂ C ₅ H ₃ N	EtOH	50	-2.81	0.75	0.09	0.966	3	<i>i</i>
	EtOH	60	-2.82	0.25	0.03	0.996	3	<i>i</i>
Py + 2-NO ₂ -4-ClC ₅ H ₃ N → 4-Py ⁺ -5-NO ₂ C ₅ H ₃ N	EtOH	20	-2.66	0.20	0.02	0.997	3	<i>i</i>
	EtOH	30	-2.49	0.03	0.004	0.999	3	<i>i</i>
	EtOH	40	-2.19	0.04	0.004	1.000	3	<i>i</i>
Py + 2,4-(NO ₂) ₂ C ₆ H ₃ -Cl → 2,4-(NO ₂) ₂ C ₆ H ₃ -Py ⁺	EtOH	50	-2.84	0.33	0.04	0.993	3	<i>i</i>
Py + MeI → PyMe ⁺ I ⁻	PhNO ₂	30	-1.27	0.58	0.11	0.663	8	<i>j</i>
Py + EtI → PyEt ⁺ I ⁻	PhNO ₂	60	-1.28	0.48	0.09	0.736	8	<i>j</i>
Py + Me ₂ CHI → PyCHMe ₂ ⁺ I ⁻	PhNO ₂	80	-1.07	0.36	0.07	0.772	8	<i>j</i>
Py + CH ₂ =CHCH ₂ Br → PyCH=CHCH ₂ ⁺ Br ⁻	MeNO ₂	60	-2.53 ^k	0.31	0.36	0.951	8	<i>l</i>
	MeNO ₂	60	-1.42 ^m	0.06	0.69	0.993	5	<i>j</i>

TABLE V—continued

Reaction ^a	Solvent	T° C	ρ^a	s_ρ^b	s^c	r^d	n^e	Reference
Py + $\text{H}_2\text{C} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{CHMe} \rightarrow$	H ₂ O	30	-0.56	0.14	0.07	0.942	4	<i>n</i>
Py + Ag ⁺ → Py ⁺ -Ag	H ₂ O	25	-2.07	0.33	0.36	0.901	11	<i>o</i>
Hydrolysis of bis(ethylenediamine)pyridine-chlorocobalt(III) ions	H ₂ O; pH 1.2	50	-0.47	0.11	0.02	0.951	4	<i>p</i>
	H ₂ O; pH 9.18	25	0.40	0.16	0.03	0.870	4	<i>p</i>
Shift of 2689 cm ⁻¹ band of MeOD ^q	Py	25	-0.019	0.002	0.0005	0.990	4	<i>r</i>
Heat of mixing of Py with MeCl	—	25	-0.74	0.12	0.03	0.976	4	<i>r</i>
Py + C ₆ H ₅ CO ₃ H → PyO	H ₂ O	25	-2.23 ^r	0.26	0.12	0.980	5	<i>t</i>
p <i>K</i> of PyO	H ₂ O	~ 25	1.89	0.07	0.20	0.992	13	<i>u</i>
Shift of 1510 cm ⁻¹ band of ethylene in <i>trans</i> -PyO-ethylene-dichloroplatinum(II) complexes ^q	Nujol mull	—	0.018 ^s	0.005	0.008	0.998	6	<i>v</i>
Shift of 1235 cm ⁻¹ band of pyridine 1-oxide in <i>trans</i> -PyO-ethylene-dichloroplatinum(II) complexes ^q	Nujol mull	—	0.030 ^w	0.005	0.007	0.940	6	<i>v</i>
Shift of 1242 cm ⁻¹ band of PyO ^q	Nujol mull	—	0.029 ^w	0.003	0.004	0.978	6	<i>u</i>
Shift of 1242 cm ⁻¹ band of PyO ^q	solid	—	0.033 ^x	0.001	0.008	0.998	4	<i>y</i>
Shift of 1270 cm ⁻¹ band of PyO ^q	CS ₂	—	0.033 ^x	0.002	0.02	0.997	4	<i>y</i>
Change of force constant in PyO ^z	—	—	6.69 ^x	0.24	0.27	0.999	4	<i>y</i>
Polarographic reduction potentials of PyO	H ₂ O	25	0.47	0.02	0.03	0.983	17	<i>z</i>
Shift of the 3645 cm ⁻¹ band of MeOH ^q with PyO	CCl ₄	—	-0.033	0.005	0.006	0.990	14	<i>aa</i>
Free energy of adsorption of Py on Al ₂ O ₃ from pentane		24	-2.46	0.14	0.16	0.987	13	<i>bb</i>

^a Py refers to the series of substituted pyridines undergoing reaction, i.e., $\text{Py} = \text{RC}_5\text{H}_4\text{N}$ where R is a substituent.

^b The standard error of ρ .

^c The standard deviation from the regression line.

^d The correlation coefficient.

^e The number of compounds entering into the determination of ρ .

^f Based on ΔpK values; cf. Table IV.

^g The following substituents listed in Table IV were omitted in the determination of ρ : 3-SO_3^- , 4-SO_3^- , 3-CO_2^- , and 4-CO_2^- . For these ionic substituents a strong dependence of the σ -values calculated on ionic strength was observed, and it was impossible to extrapolate to zero ionic strength; cf. H. Zollinger, W. Büchler, and C. Wittwer, *Helv. Chim. Acta* **36**, 1711 (1953).

^h Cf. Table IV.

ⁱ E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.* 3392 (1953); R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *ibid.* 437 (1952).

^j H. C. Brown and A. Cahn, *J. Am. Chem. Soc.* **77**, 1715 (1955).

^k Calculated from *meta* substituent constants only.

^l K. Clarke and K. Rothwell, *J. Chem. Soc.* 1885 (1960).

^m Calculated from *para* substituent constants only.

ⁿ J. Hansen, *Svensk Kem. Tidskr.* **67**, 246, 263 (1955).

^o R. K. Murmann and F. Basolo, *J. Am. Chem. Soc.* **77**, 3484 (1955).

^p F. Basolo, J. G. Bergmann, R. E. Meeker, and R. G. Pearson, *J. Am. Chem. Soc.* **78**, 2676 (1956).

^q To make ρ and sp dimensionless, $\Delta\nu/\nu^0$ was correlated with σ , where $\Delta\nu$ is the band shift and ν^0 is the frequency of the un-substituted compound; cf. Ref. 3.

^r M. Tamres, S. Searles, E. M. Leighly, and D. W. Mohrman, *J. Am. Chem. Soc.* **78**, 2676 (1956).

^s σ^- -Values were used for electron-withdrawing substituents, σ^+ -values for electron-releasing substituents.

^t A. Dondoni, G. Modena, and P. E. Todesco, *Gazz. Chim. Ital.* **91**, 613 (1961); G. Modena and P. E. Todesco, *ibid.* **90**, 1, 702 (1960).

^u H. H. Jaffé, *J. Org. Chem.* **23**, 1790 (1958).

^v S. I. Shupack and M. Orchin, *J. Am. Chem. Soc.* **85**, 902 (1963).

^w σ^+ -Values were used in the correlation.

^x To make ρ and sp dimensionless, $\Delta k/k^0$ was correlated with σ , where Δk is the force constant difference and k^0 is the force constant of the unsubstituted compound.

^y G. Costa and P. Blasina, *Z. Physik. Chem. (Frankfurt)* **4**, 24 (1955).

^z T. Kubota, private communication (1963).

^{aa} H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **7**, 791 (1959).

^{ab} L. R. Snyder, *J. Phys. Chem.*, in press.

of a few β - and γ -substituted pyridines. Irving and daSilva⁵⁸ have shown that these data can be correlated by the Hammett equation. In another study, Basolo and co-workers⁵⁹ have investigated the rates of hydrolysis of bis(ethylenediamine)pyridinechlorocobalt(III) ion and three of its analogs with substituted pyridines by water and hydroxide ion. The rates are relatively insensitive to substituents and do not follow the Hammett equation at all well; the ρ values for the water and hydroxide reactions have opposite signs.

Charton^{59a} has recently examined substituent effects in the *ortho* position in benzene derivatives and in the α -position in pyridines, quinolines, and isoquinolines. He concludes that, in benzene derivatives, the effects in the *ortho* position are proportional to the effects in the *para* position (σ_p). However, he finds that effects of α -substituents on reactions involving the sp^2 lone pair of the nitrogen atoms in pyridine, quinoline, and isoquinoline are approximately proportional to σ_m -values, or possibly to inductive effects (Taft's σ_1). He also notes that the effects of substituents on proton-deuterium exchange in the *ortho* position of substituted benzenes are comparable to the effects of the same substituents in the α -position of the heterocycles.

Finally, two sets of physical properties have been correlated by the Hammett equation. Sharpe and Walker⁶⁰ have shown that changes in dipole moment are approximately linearly correlated with σ -values, and Snyder^{60a} has recently correlated the free energies of adsorption of a series of substituted pyridines with σ -values. All the reaction constants for the series discussed are summarized in Table V.

B. REACTIONS AT SIDE-CHAINS ATTACHED TO HETEROATOMS

The first suggestion that the reactivity of a group attached to a heteroatom may be treated in terms of the Hammett equation relates to the basicities of pyridine 1-oxides.⁴⁹ The original correlation using σ^- -values was fair, but strongly electron-repelling substituents deviated substantially from the straight lines. When Brown's σ^+ -values became available it was soon recognized that use of these constants for the electron-repelling substituents greatly improved the correlation.⁴⁸ This reaction series was thus the first one which required σ^- -values for electron-withdrawing substituents and σ^+ -values for electron-repelling substituents. This somewhat curious circumstance may be rationalized since it is known that the following resonance structures are important in pyridine 1-oxide⁴⁵:

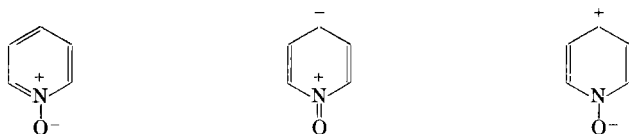
⁵⁸ H. Irving and J. J. R. F. daSilva, *Proc. Chem. Soc.* 250 (1962).

⁵⁹ F. Basolo, J. G. Bergmann, R. E. Meeker, and R. G. Pearson, *J. Am. Chem. Soc.* **78**, 2676 (1956).

^{59a} M. Charton, *J. Am. Chem. Soc.*, in press.

⁶⁰ A. N. Sharpe and S. Walker, *J. Chem. Soc.* 4522 (1961).

^{60a} L. R. Snyder, *J. Phys. Chem.*, in press.



Interestingly enough, the ρ -value is very similar to that applicable to the acid-base equilibria of phenols, which is a reaction in which both reactant and product are isoelectronic with the corresponding species in the reaction under consideration.

Extensive data are available on the N—O stretching frequency at about 1265 cm^{-1} in substituted pyridine N-oxides. Unfortunately the data from different laboratories are not readily comparable since they were obtained under different conditions, particularly in different solvents; in addition, in the realm of the small differences generally encountered in infrared spectra, differences between instruments and

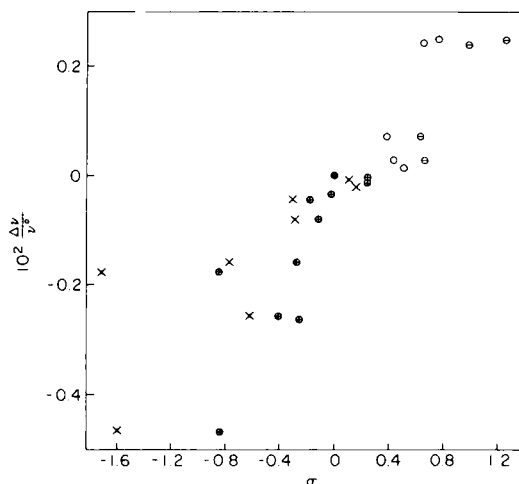


FIG. 3. The N—O stretching frequencies of 4-substituted pyridine 1-oxides in chloroform; cf. ref. 61. Solid circles if $\sigma = \sigma^+ = \sigma^-$; crossed circles, $\sigma = \sigma^+$; barred circle, $\sigma^- (\neq \sigma)$; open circle, $\sigma = \sigma^-$; cross, $\sigma^+ (\neq \sigma)$.

in experimental technique between different laboratories make combination of results from separate groups even more uncertain than is already the case with rate and equilibrium data. For the stretching frequencies of the NO bond one might, by comparison with similar data in other series, anticipate the need for using σ^+ -constants, or even σ^+ - and σ^- -constants. Which constants apply is difficult to decide, as will be seen from the following paragraphs.

The longest series of infrared frequencies is that reported by Katritzky and Gardner⁶¹ and is restricted to γ -substituted derivatives in chloroform solution. These data are plotted in Fig. 3 against the

⁶¹ A. R. Katritzky and J. R. Gardner, *J. Chem. Soc.* 2192 (1958).

various types of σ -constants, and it is seen immediately that they do not fit any one set well. A decision as to which set is best followed is complicated by the fact that not all types of σ -values are available for each group treated. In addition, a statistical analysis is of relatively little value because the uncertainties in the fit are so large. This relatively large scatter of data is, of course, commonly encountered in the treatment of infrared spectral data since the differences observed often do not greatly exceed experimental accuracy and because, in addition, such factors as Fermi resonances may seriously complicate matters.

Another rather extensive series of similar data, obtained using CS₂ solutions and nujol mulls, has been published by Shindo (Fig. 4).⁴⁷ His series include considerable data for β -substituted compounds, for which the question of a choice of substituent constants does not arise. His data also show considerable scatter but seem to suggest strongly that σ^+ -values are indicated for $+M$ substituents and normal σ -values for $-M$ substituents. The conclusion is confirmed by the short series of similar data reported by Costa and Blasina⁶² and by Shupack and Orchin.⁶³ The data of the latter authors for the NO frequencies in *trans*-ethylene pyridine N-oxide dichloroplatinum(II) complexes are also moderately well correlated with σ^+ -values.

Shindo^{63a} has extended the correlation of pyridine N-oxide N—O stretching frequencies to the pyrazine mono- and di-N-oxides, by assuming $\sigma_p(\text{>N}) = 0.93$ and $\sigma_p(\text{>N}^+—\text{O}^-) = 0.25$ (presumably σ_p^+), and to substituted pyrimidine N-oxides.

Shindo^{63b} studied the hydrogen-bonding ability of a fairly long series of substituted pyridine 1-oxides with methanol in chloroform solution and found that the OH frequency of the hydrogen-bonded OH group in methanol is well correlated with the σ -values. For four compounds, the intensity of the same band is also well correlated. In a similar study the OH frequencies of phenol vary monotonically with the σ -values, but not in a linear fashion.

Kubota and Miyazaki^{63c} studied the polarographic reduction of pyridine N-oxides and found a satisfactory correlation with the σ -values. The values increase with increasing pH.

⁶² G. Costa and P. Blasina, *Z. Physik. Chem. (Frankfurt)* **4**, 24 (1955).

⁶³ S. I. Shupack and M. Orchin, *J. Am. Chem. Soc.* **85**, 902 (1963).

^{63a} H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **8**, 33 (1960).

^{63b} H. Shindo, *Chem. Pharm. Bull. (Tokyo)* **7**, 791 (1959).

^{63c} T. Kubota and H. Miyazaki, *Bull. Chem. Soc. Japan*, in press.

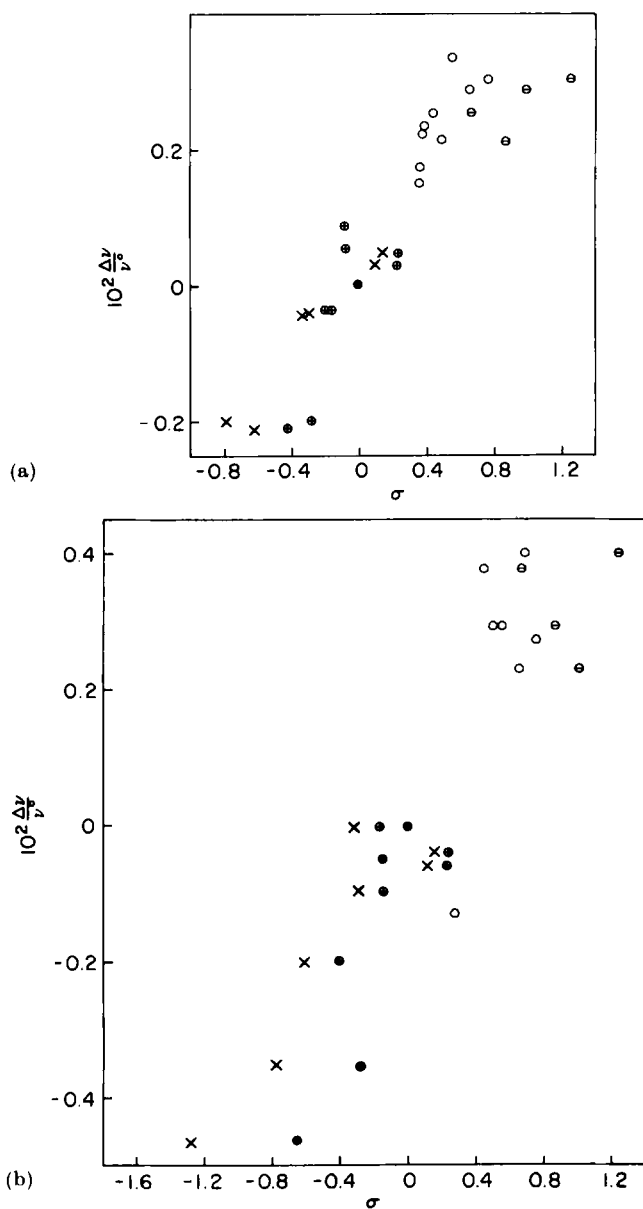


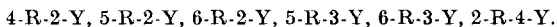
FIG. 4. The N—O stretching frequencies of substituted pyridine 1-oxides (a) in CS_2 and (b) in Nujol mull; cf. ref. 47. Solid circles if $\sigma = \sigma^+ = \sigma^-$; crossed circles, $\sigma = \sigma^+$; barred circle, $\sigma^- (\neq \sigma)$; open circle, $\sigma = \sigma^-$; cross, $\sigma^+ (\neq \sigma)$.

Pyridine 1-oxide, like pyridine, can act as a ligand in transition metal complexes, but unfortunately good stability constants are not known. However, Shupack and Orchin⁶³ have found that the C=C stretching frequency of the ethylene ligand in trans-ethylene pyridine 1-oxide dichloroplatinum(II) varies linearly with the pK and hence with the σ -value (σ^+ or σ^- , respectively) of substituents in the pyridine oxide. The data for the above reaction series are included in Table V.

IV. Transmission of Substituent Effects through Heterocyclic Systems

A. SIX-MEMBERED RING SYSTEMS

The problems encountered in any attempt to treat the transmission of the effects of one substituent in a disubstituted heterocycle through the heterocyclic nucleus to a reaction site in the other substituent (i.e. the side-chain) are enormous, and it is consequently not surprising that relatively little work has been done in this area. First, while in benzene derivatives there are three "positions," i.e. three relations between substituent and reacting side-chain to be considered, the number of complexities is much greater in heterocycles. Thus, e.g., in pyridine alone, after elimination of the orientations involving a vicinal relationship between substituent R and the side-chain Y⁶⁴ to which no Hammett-type relation is likely to be applicable, the following cases should be considered:



In the cases 6-R-3-Y and 5-R-2-Y, the relation of R to Y corresponds to the *para* relation in benzene. When Y is in the 4-position, only *meta*-type (2-R or 6-R) substituents are possible. With R in the 2-position, aside from the one *para*-type relation (5-R-2-Y), two *different meta*-type relations (4-R- and 6-R-2-Y) are possible, and the reactivity need not be the same for these two. Two ways suggest themselves to overcome this difficulty: One might attempt to define separate σ -values for substituents, depending not only on the relative position with respect to the side-chain, as in σ_m and σ_p , but also in relation to the heteroatom; thus, for 6-R-3-Y one would have a $\sigma_{\alpha,p}$ -value and for 5-R-2-Y a $\sigma_{\beta,p}$ -value. This system would still require distinction in the case of $\sigma_{\alpha,m}$ between $\sigma_{\alpha,m\alpha}$ for 6-R-2-Y and $\sigma_{\alpha,m\gamma}$ for 2-R-4-Y. With this system a single ρ -value would suffice for any type of reaction, but the very large

⁶⁴ Throughout, R will be used to designate the rate (or equilibrium) affecting substituent, Y the reacting side-chain.

number of σ -values (six for each substituent of which at least two, $\sigma_{\alpha,p}$ and $\sigma_{\beta,p}$, could occur as σ , σ^+ , or σ^-) would require extremely extensive experimental material before any reasonable test of the correlation could be made. No such extensive data are presently available.

The alternate procedure, which has actually been applied, is to define separate reaction constants (ρ_α , ρ_β , and ρ_γ), depending on the location of the side-chain relative to the heteroatom, and to make separate correlations. Here, the remaining uncertainty is that for 2-Y there are the two *meta*-type positions mentioned above. This is the approach which has been used successfully in the few reported correlations to be discussed below.

A further complication arises out of the fact that of all the orientations discussed only one, 5-R-3-Y, does not involve a vicinal relationship between at least two of the three structural features—substituent, side-chain, and heteroatom. In the cases of 4-R- and 5-R-2-Y the problem of vicinal relations appears not too serious, since this relation is equivalent to the problem of the constant *ortho* substituent.⁶⁵ For this situation it was shown that the “constant *ortho* substituent,” i.e., in this case the heteroatom, may make a contribution to the substituent-independent term ($\log k^\circ$) but generally leaves the reaction constant (ρ) unaffected. Where the substituent, however, is *alpha* to the heteroatom it appears likely that its electronic structure, and hence its σ -values, may be substantially affected. This appears particularly likely for large substituents and especially for those which can form a hydrogen bond with the heteroatom, such as COOH.

In the manner outlined, a few attempts have been made to apply the Hammett equation to the transmission of substituent effects in the pyridine series.⁶⁶ In the alkaline hydrolysis of 5-substituted ethyl picolinate (5-R-2-COOEt) in 85% ethanol at 25, 35, and 45°, the reaction constants are about 60% as large as those in the corresponding benzene series; the overall fit to the Hammett equation, however, is at best fair, since out of four points (R = Et, H, I, Ac) one (Ac) deviates widely.

Using the pK_a values of the 5-substituted picolinic acids (5-R-2-COOH) and the 6-substituted nicotinic acids (6-R-3-COOH), in 50% ethanol at 25°, considerably better correlations are observed, with $\rho = 3.31$ and 1.60, respectively.⁶⁶ The transmission through the

⁶⁵ H. H. Jaffé, *Science* **118**, 246 (1953); cf. also Ref. 3.

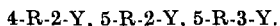
⁶⁶ Y. Otsuji, Y. Koda, and J. Hirai, *Nippon Kagaku Zasshi* **80**, 1293 (1959).

pyridine rings relative to the benzene series is considerably greater. It has been suggested that this is due to a tautomeric equilibrium between the neutral acid and zwitterion forms, so that the measured substituent effects reflect a combination of effects on the pK_a values of the carboxylic acid group and of the pyridinium ion, for which the value of ρ is much larger. This explanation seems improbable in the light of the behavior of a tautomeric system under the effect of substituents, which is described in Section VI. However, considerably more work needs to be done before this conclusion can be discarded.

One other attempt at a similar treatment of data merits mention. Taylor *et al.*⁶⁷ have measured the pK_a values of a series of 4-substituted nicotinic acid N-oxides. Curiously enough, a good fit to the Hammett equation is observed in spite of the fact that the substituent and the carboxyl group are vicinal. The authors' suggestion that the reaction observed is the dissociation of a *N*-hydroxypyridinium-3-carboxylate is rendered unlikely by the finding of Jaffé and Doak⁴⁹ that nicotinic acid N-oxide exists almost completely in the neutral form. It also seems difficult to explain how a 3-COO⁻ group could cause the pK value of the *N*-hydroxypyridinium ion to increase about 0.8 to 2.74. The ρ -value of 2.35 seems slightly high compared with that of the pyridine N-oxides, $\rho = 1.89$. On the other hand, it seems curious that the effect of a series of six compounds with substituents *ortho* to a reacting carboxyl group should correlate well with *para* σ -values, particularly since most of the substituents probably are hydrogen-bonded to the carboxyl group. The data remain unexplained.

B. FIVE-MEMBERED RING SYSTEMS

The problem of applying the Hammett equation to five-membered ring systems has been extensively treated by Imoto and co-workers.^{38, 68} All the problems discussed in the preceding section naturally recur; the possible orientations not involving a vicinal relation between substituent and side-chain are:



⁶⁷ J. S. Driscoll, W. Pfeleiderer, and E. C. Taylor, *J. Org. Chem.* **26**, 5230 (1961).

⁶⁸ E. Imoto, Y. Otsuji, and J. Hirai, *Nippon Kagaku Zasshi* **77**, 804 (1956); E. Imoto, Y. Otsuji, and H. Inoue, *ibid.* **77**, 809 (1956); E. Imoto, R. Motoyama, and H. Kakiuchi, *ibid.* **77**, 812 (1956); E. Imoto and R. Motoyama, *Bull. Osaka Prefect. Univ.* **2A**, 127 (1954).

Only 4-R-2-Y does not involve a vicinal relation between substituent and heteroatom and, hence, is probably the "best" case for the present purpose.

The relative orientation of the substituent and the side-chain—in terms of the benzene *ortho*, *meta*, *para* scheme—is an added complication. Following the practice first established by Hammett^{1,2} in treating the furoic acids,³⁴ it is customary to treat the heteroatom (>NH, >S, >O) as if it had replaced a vinyl group (—CH=CH—) in benzene. Thus, the 4-R-2-Y and 5-R-3-Y relationships become *meta*, and 5-R-2-Y becomes *para*.

Using these assumptions and conventions, Imoto and co-workers⁶⁸ have correlated a number of series of reactions of thiophenes and furans. The reactions studied are the acid-base equilibria (pK_a values) and the acid catalyzed methylations (thiophenes only) of thiophene- and furan-carboxylic acids and the alkaline hydrolyses of their ethyl esters; the side-chain bromination of the α -acetylthiophenes, and the α -mercuration of thiophenes; and the polarographic half-wave potentials of the methyl esters of thiophene- and furan-carboxylic acids and of nitrothiophenes. The pK_a values were determined and the ester hydrolyses studied for all three substitution orientations in the thiophene series. For the 4-R-2-Y and 5-R-2-Y series, the ρ -values do not appear significantly different and the data could probably be combined into a single series; unfortunately, however, no limits of accuracy are reported for the ρ -values, and some of the raw data are not readily available so recalculation is not easily possible. For the 5-R-3-Y series the ρ -values deviate considerably from the other values; however, whereas they are higher for the pK_a values, they are lower for the ester hydrolyses, and it is possible that the differences are neither systematic nor significant.

The authors have compared in every case the ρ -values for the heterocyclic series (ρ_H) with the corresponding ρ -value for the benzene series (ρ_B) under identical conditions. The ratios ρ_H/ρ_B in the thiophene series vary between 0.63 and 1.34, with the two extreme values applying to the 5-R-3-Y systems. For the other systems the variation is between 0.83 and 1.20 with an average value of 0.99. The three furan-system values, all for 5-R-2-Y, are more divergent, between 0.89 and 1.39, with an average of 1.15, apparently slightly higher, than in the thiophene system.

Gronowitz and Gestblom⁶⁹ have reported the methyl proton

⁶⁹ S. Gronowitz and R. Gestblom, *Arkiv Kemi* **18**, 513 (1961).

TABLE VI

REACTION SERIES INVOLVING THE TRANSMISSION OF SUBSTITUENT EFFECTS THROUGH HETEROCYCLIC RINGS

Reaction	Solvent	$T^{\circ}\text{C}$	ρ	s_{ρ}^a	s^b	r^c	n^d	Reference
pK of 5-R-thiophene-2-carboxylic acids	H ₂ O	25	1.10	0.10	0.07	0.988	5	<i>e</i>
pK of 5-R-thiophene-3-carboxylic acids	H ₂ O	25	1.31	0.06	0.04	0.995	4	<i>f</i>
pK of 4-R-thiophene-2-carboxylic acids	H ₂ O	25	0.97	0.08	0.05	0.990	5	<i>f</i>
Base hydrolysis of ethyl 5-R-thiophene-2-carboxylates	85% EtOH	30	1.87	0.24	0.17	0.983	4	<i>e</i>
Base hydrolysis of ethyl 5-R-thiophene-2-carboxylates	85% EtOH	40	1.86	0.30	0.22	0.975	4	<i>e</i>
Base hydrolysis of ethyl 5-R-thiophene-3-carboxylates	85% EtOH	25	1.63	0.07	0.04	0.998	4	<i>f</i>
Base hydrolysis of ethyl 4-R-thiophene-2-carboxylates	85% EtOH	25	2.88	0.17	0.11	0.996	4	<i>f</i>
Base hydrolysis of ethyl 4-R-thiophene-2-carboxylates	85% EtOH	35	2.88	0.15	0.10	0.997	4	<i>f</i>

p <i>K</i> of 5-R-2-furoic acids	H ₂ O	25	1.40	0.11	0.06	0.988	6	<i>g</i>
Base hydrolysis of ethyl 5-R-2-furoates	85% EtOH	25	3.07	0.13	0.09	0.998	4	<i>e</i>
Acid catalyzed methanolysis of 5-R-thiophene-2-carboxylic acids	MeOH	45	-0.34	0.10	0.07	0.884	5	<i>e</i>
E _{1/2} of 2-NO ₂ -5-R-thiophenes	H ₂ O; pH 3.10	—	0.20 ^a	0.06	0.05	0.718	12	<i>i</i>
E _{1/2} of 2-NO ₂ -5-R-thiophenes	H ₂ O; pH 2.9	25	0.30 ^a	0.01	0.01	0.999	4	<i>j</i>
E _{1/2} of 2-NO ₂ -5-R-thiophenes	H ₂ O; pH 5.0	25	0.40 ^a	0.02	0.01	0.997	4	<i>j</i>
E _{1/2} of 2-NO ₂ -5-R-thiophenes	H ₂ O; pH 7.6	25	0.46 ^a	0.02	0.01	0.998	4	<i>j</i>
Carbonyl stretching frequency in 2-acetyl-5-R-thiophenes	CCl ₄	—	0.0075	0.001	0.002	0.951	6	<i>k</i>

^a The standard error of ρ .

^b The standard deviation from the regression line.

^c The correlation coefficient.

^d The number of compounds entering into the determination of ρ .

^e E. Imoto, Y. Otsuji, and J. Hirai, *Nippon Kagaku Zasshi* **77**, 804 (1956); E. Imoto, Y. Otsuji, and H. Inoue, *ibid.* **77**, 809 (1956); E. Imoto, R. Motoyama, and H. Kakiuchi, *ibid.* **77**, 812 (1956); E. Imoto and R. Motoyama, *Bull. Osaka Prefect. Univ.* **2A**, 127 (1954).

^f Y. Otsuji, T. Kimura, Y. Sugimoto, and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1021 (1959).

^g W. E. Catlin, *Iowa State Coll. J. Sci.* **10**, 65 (1935).

^h ρ -Values are given in volts.

ⁱ Cf. ref. 71.

^j E. Imoto, R. Motoyama, and H. Kakuchi, *Bull. Naniwa Univ.* **A3**, 203 (1955).

^k Y. Otsuji and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1199 (1959).

magnetic resonance shifts for a series of 5-substituted 2-methylthiophenes and for a few 3-methylthiophenes. A very rough correlation with σ -values can be observed from their data, but the relation is far from convincing. This and other related work on the application of the Hammett equation to thiophenes has been reviewed recently.^{69a}

The carbonyl stretching vibrations in a series of 5-substituted 2-acetylthiophenes are reasonably well correlated by σ^+ -values.⁷⁰

Tirouflet and co-workers⁷¹ have also found that the polarographic half-wave potentials of 5-substituted 2- and 3-nitrothiophenes are well correlated with the corresponding σ -values and with the half-wave potentials of the corresponding nitrobenzenes. Here again, the ρ -values are substantially equal in the thiophene and benzene series. The same authors have found similar correlations for the 5-substituted 2- and 3-nitropyrroles. In this case the ρ_H/ρ_B ratio is substantially greater than one, indicating that the order of transmission of electronic effects is $-\text{HC}=\text{CH}- \approx -\text{S}- < -\text{O}- < -\text{NH}-$. This work appears to represent the only known application of the Hammett equation to a pyrrole series.

Imoto and co-workers⁶⁸ have also studied the pK values of substituted thiazolecarboxylic acids and the alkaline hydrolysis of their ethyl esters, each in three relative positions (2-R-4-Y, 2-R-5-Y, and 5-R-2-Y). In the case of the pK values, the ρ -values are far from constant, varying from 0.83 to 2.35. This variation is likely to be due to the intervention of tautomeric equilibria and of hydrogen bonds. The ρ -ratios for the three sets of ester hydrolyses are roughly constant (0.61–0.73), and, assuming that the introduction of two heteroatoms leads to cumulative (multiplicative) effects on the transmission, this result is of the same order of magnitude as the product of the $>\text{S}$ and $\geq\text{N}$ values discussed above, i.e. 1.0 and 0.6, respectively. The lowest value for the pK (0.83) for the 2-R-5-COOH series is also of the same order of magnitude. All the available reaction constants are summarized in Table VI.

^{69a} S. Gronowitz, *Advan. Heterocyclic Chem.* **1**, 80–82 (1963).

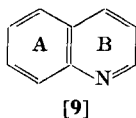
⁷⁰ Y. Otsuji and E. Imoto, *Nippon Kagaku Zasshi* **80**, 1199 (1959).

⁷¹ J. Tirouflet, *XV Congr. Intern. Quim. Pura Apl.* (Lisbon), Vol. I, 1957, p. 1; "Advances in Polarography," p. 740, Pergamon Press, London, 1960; J. Tirouflet and M. Person, *Ric. Sci.* **5** Suppl. "Contributi teorici e Sperimentali di polarografia" (1960); J. Tirouflet and J. P. Chané, *Compt. Rend.* **245**, 80, 500 (1957); P. Fournari, Dissertation, Dijon, 1961.

V. Polycyclic Compounds

A. FUSED SIX-MEMBERED RINGS

The application of the Hammett equation to bicyclic aromatic compounds of the quinoline and isoquinoline type may be envisaged in several ways. In quinoline, e.g., the homocyclic ring (*A* in **9**) may be



considered as the "benzene" ring, to which the Hammett equation is applicable. On this basis, a substituent in the *A*-ring, and particularly in the 6- or 7-position, might be treated as a substituent affecting the reactivity of the nitrogen atom, or a side-chain attached to the *B*-ring could be considered as a normal Hammett relation involving a reaction site attached to the aromatic ring (*A*) at two points.⁷² This treatment uses Eq. (3), where ρ_1 and ρ_2 refer to transmission through the two links between the *A*-ring and the reaction site, and σ_1 and σ_2 are the appropriate σ -values.

$$\log(k/k^0) = \sigma_1\rho_1 + \sigma_2\rho_2 \quad (3)$$

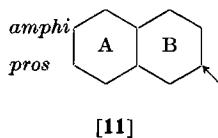
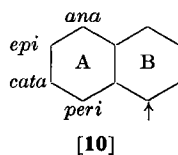
On the other hand, the Hammett equation may be applied to the *B*-ring, and the entire *A*-ring may be considered as a substituent. This is equivalent to Hammett's original proposal of including the β -C₄H₄ (β -naphthyl) group as a substituent and is likely to be useful for reaction at the 2-position or at side-chains attached to the 2-position. When, however, the reaction occurs at the 1-position, or at a side-chain attached thereon, there appears an *ortho* substituent, and the Hammett equation in its simple form is not applicable. It has been shown, however,⁶⁵ that a *constant ortho* substituent, although affecting the value of the reaction rates, does not have any effect on the reaction constants (ρ). Consequently, on comparing the reactivity of quinoline with one of its derivatives substituted on the *A*-ring, the steric effect of the fused ring drops out. For this reason it has been suggested^{73, 74} that a substituent constant may be assigned to any substituent in any one of the positions of the *A*-ring, relative to a reaction occurring at

⁷² H. H. Jaffé, *J. Am. Chem. Soc.* **76**, 4261 (1954).

⁷³ P. R. Wells and E. R. Ward, *Chem. Ind. (London)* 528 (1958).

⁷⁴ E. Baciocchi, G. Illuminati, and G. Marino, *J. Am. Chem. Soc.* **80**, 2270 (1958).

one or the other site of the *B*-ring. Substitution may be in any one of the four possible positions (5, 6, 7, or 8), and for each of these, the reaction site may be at, or attached to, the 1- or 2-position. The 5-1, 6-1, 7-1, and 8-1 relations have been named *ana*-, *epi*-, *cata*-, and *peri*-, respectively, and the 6-2 and 7-2, *amphi*- and *pros*-, respectively, as shown in **10** and **11**; because these labels are relatively



rarely used in the literature and unfamiliar to many workers, and since two relations do not seem to have been named, we will use the 5-1, etc. notation for a 5 substituent relative to a 1 reaction site. In the 5-1, 5-2, and 8-2 relations the substituent and the *B*-ring are likely to undergo some serious steric interaction; it is probable that this interaction will however, be constant from one reaction series to another, so that σ -values may well be meaningful. The 8-1 (*peri*-) relation, with substituent and reaction center adjacent, is probably so strongly affected by steric effects that σ -values for this position are unlikely to be meaningful.

Both of these approaches have been attempted, and both are substantially equivalent for heterocyclic (e.g. quinoline and isoquinoline) and homocyclic (naphthalene) systems. Consequently, in the subsequent discussion it is fruitful to include the available work on naphthalene derivatives. In the case of the fused six-membered rings, Eq. (3) is not applied because it does not permit treatment of the 5- and 8-positions, and the available series as a whole are too short to make this treatment useful.

The first reaction series to be considered are the basicities of the various quinolines. Baciocchi and Illuminati⁷⁵ have demonstrated that the pK values of quinolines substituted in the *B*-ring follow the Hammett equation well; if ΔpK , i.e., the difference between the pK values of substituted and unsubstituted compounds, is plotted against σ , the quinoline points fall on the same line as the pyridine points, as shown in Fig. 5, so that the ρ -values for the two series are identical.

⁷⁵ E. Baciocchi and G. Illuminati, *Gazz. Chim. Ital.* **87**, 981 (1957).

This conclusion is further confirmed by Bryson's data⁷⁶ on the basicities of quinolines and isoquinolines substituted in the 3- and 4-positions, respectively, i.e., in the positions *meta* to the aza nitrogen, which are correlated with σ_m -values with $\rho = 5.46 \pm 0.31$, $n = 7$, $r = 0.992$, $s = 0.21$ and $\rho = 5.57 \pm 0.12$, $n = 5$, $r = 0.999$, $s = 0.08$, respectively. Baciocchi and Illuminati have also reported the basicities of a series of 6-substituted 4-chloroquinolines. By comparison with the

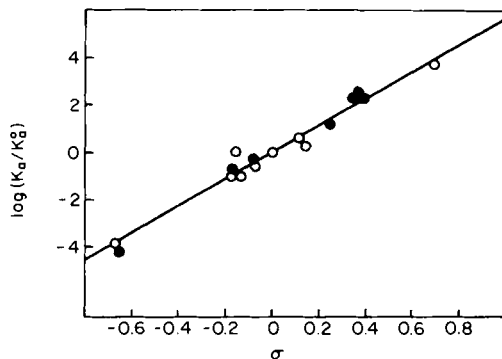


FIG. 5. The relative pK -values of 3- and 4-substituted pyridines (open circles) and quinolines (full circles); cf. ref. 75. Reprinted by permission.

data of Knight *et al.*,⁷⁷ a given substituent was shown to produce the same effect on the basicity of quinoline and its 4-chloro derivative.⁷⁵ From these data and using the ρ -value from the pyridine series, as justified by the correlation shown in Fig. 5, σ -values for the 6-1 (*epi*-) position have been derived and are listed in Table VII. In a later paper,⁷⁴ the work on the 4-chloroquinolines was extended to 7-substituted compounds, and 7-1 (*cata*-) σ -values are given.

In the same series of compounds,^{74,78} i.e. the 4-chloroquinolines, rates of methoxydechlorination are treated in a similar manner, yielding a further set of 6-1 (*epi*-) and 7-1 (*cata*-) substituent constants, which are listed in Table VII. The necessary ρ -value was obtained by plotting the rate data against the pK data and using the slope of the

⁷⁶ A. Bryson, *J. Am. Chem. Soc.* **82**, 4871 (1960).

⁷⁷ W. K. Miller, S. B. Knight, and A. Roe, *J. Am. Chem. Soc.* **72**, 4763 (1950); S. B. Knight, R. H. Wallick, and J. Bowen, *ibid.* **76**, 3780 (1954); S. B. Knight, R. H. Wallick, and C. Balch, *ibid.* **77**, 2577 (1955).

⁷⁸ G. Illuminati and G. Marino, *J. Am. Chem. Soc.* **80**, 1421 (1958).

TABLE VII
SIGMA VALUES IN FUSED RING SYSTEMS

Substituent	Type of substitution*								Type ^a	Reaction ^b
	5-1	6-1	7-1	8-1	5-2	6-2	7-2	8-2		
NO ₂	0.39	0.38	0.44	0.41	0.33	0.34	0.31	0.32	σ	1
	0.68	0.53	0.35	0.46	0.52	0.63	0.55	0.23	σ	2
	—	0.44	0.39	—	—	—	—	—	σ	3
	0.43	—	—	—	—	—	—	—	σ	4
	0.49	—	—	—	0.42	—	—	0.33	σ	5
	0.50	0.48	—	—	—	—	—	—	σ	6
	—	—	—	—	—	—	0.40 ^c	—	σ	7
	—	—	—	—	—	—	0.41 ^c	—	σ	8
	0.42	—	—	—	0.22	0.60	0.22	0.54	σ	9
	0.40	0.28	0.39	0.41	0.34	0.49	0.35	0.45	σ	10
	0.36	0.30	0.43	—	0.28	0.52	0.28	0.40	σ	11
	0.67	0.52	—	—	—	—	—	—	σ	12
	—	0.35	0.45	0.15	—	0.69	0.50	—	σ	13
Cl	—	0.16	0.16	—	—	—	—	—	σ	14
	—	0.16	0.14	—	—	0.19	0.24	—	σ	13
	0.22	0.14	0.19	0.32	—	—	—	—	σ	17
	—	—	0.09	—	—	—	—	—	σ	4
	—	—	0.11	—	—	—	—	—	σ	5
	—	0.17	—	—	—	—	—	—	σ	3
	0.30	—	—	—	—	0.30	—	—	σ	15

Br	—	0.16	0.16	—	—	—	—	σ	14
	—	0.16	0.16	—	—	—	0.25	σ^-	13
	0.23	0.16	0.19	0.32	—	—	—	σ	17
	—	0.20	0.08	—	—	—	—	σ	3
	0.24	—	—	—	—	—	—	σ	6
	0.30	—	—	—	—	—	—	σ^+	16

Table VII continues on p. 248.

* *Added in proof.* To emphasize the comparisons with naphthalene, the reaction center of each series studied has been called the 1-position. For example, in the methoxy-dechlorination of substituted 4-chloroquinolines the position to which the chlorine atom is attached is the 1-position and the nitrogen atom is the 4-position; this is in contrast to conventional numbering, where the nitrogen atom is always 1.

^a It is conceivable that for the 5-1-, 7-1-, 6-2-, and 8-2-types of substitution, separate σ^+ - and σ^- -constants might be applicable, although the evidence available now does not seem to indicate this. Accordingly, the type of σ -value applicable to various reactions is indicated.

^b (1) pK of quinolines and isoquinolines in water at 25°; cf. W. L. F. Armarego, *J. Chem. Soc.* 4094 (1960).

(2) pK of naphthoic acids in 50% butyl cellosolve at 25°; cf. E. Berliner and E. H. Winicov, *J. Am. Chem. Soc.* **81**, 1630 (1959).

(3) pK of naphthoic acids in 50% ethanol at 25°; cf. M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.* **84**, 3546 (1962).

(4) pK of naphthoic acids in 78% ethanol at 25°; cf. C. C. Price, E. C. Mertz, and J. Wilson, *J. Am. Chem. Soc.* **76**, 5131 (1954).

(5) Alkaline hydrolysis of ethyl naphthoates in 70% dioxane; cf. C. C. Price and R. H. Michel, *J. Am. Chem. Soc.* **74**, 3652 (1952).

(6) Alkaline hydrolysis of ethyl naphthoates in 85% ethanol; cf. A. Fischer, J. D. Murdock, J. Packer, R. D. Topsom, and J. Vaughan, *J. Chem. Soc.* 4358 (1957).

(7) pK of coumarilic acids in 50% ethanol at 25°; cf. ref. 82.

(8) Alkaline hydrolysis of ethyl coumarates in 85% ethanol at 35°; cf. ref. 82.

(9) Alkaline hydrolysis of acetnaphthalides in methanol; L. H. Krol, R. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.* **71**, 545 (1952).

(10) pK of naphthylamines in water at 25°; cf. ref. 74.

(11) pK of naphthols in water at 25°; cf. ref. 73 and quoted from a private communication with A. Bryson (1963).

(12) pK of naphthols in 48% ethanol at 25°; cf. ref. 71.

(13) Methoxydechlorination of 2- and 4-chloroquinolines and 2-chloroquinoxalines in methanol; cf. refs. 74, 78, 79, and 80.

(14) pK of 4-chloroquinolines in 7.7 wt.-% ethanol at 25°; cf. ref. 74.

(15) Benzoylation of naphthylamines in benzene at 25°; cf. M. Simonetta and S. Carrà, *Atti Accad. Naz. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **22**, 176 (1957); *Chem. Abstr.* **51**, 16061 (1957).

(16) Solvolysis of naphthylmethyl bromides in 90% ethanol; cf. J. B. Shoesmith and H. Rubli, *J. Chem. Soc.* 3098 (1927).

(17) pK of quinolines in 10% ethanol at 25°; cf. ref. 72.

^c Estimated using ρ -values from pK-values of furoic acids and the hydrolysis of their ethyl esters after correction for the difference in reaction conditions.

TABLE VII—*Continued*

Substituent	Type of substitution*								Type ^a	Reaction ^b
	5-1	6-1	7-1	8-1	5-2	6-2	7-2	8-2		
F	0.18	0.10	0.12	0.28	—	—	—	—	σ	17
	—	0.13	0.12	—	—	—	—	—	σ	14
	—	0.12	0.06	—	—	—	—	—	σ^-	13
Me	—	-0.05	-0.06	0.01	—	—	—	—	σ	17
	-0.04	-0.04	-0.07	-0.02	—	—	—	—	σ	1 ^a
	—	-0.04	-0.05	—	—	—	—	—	σ	14
	—	—	-0.07	—	—	—	-0.07	—	σ^-	13
	—	-0.05	-0.08	—	—	—	—	—	σ	3
	—	—	—	—	—	-0.14	-0.07	—	σ	7
	—	—	—	—	—	-0.13	-0.08	—	σ	8
	—	—	—	—	—	—	—	—	—	—
MeO	—	-0.04	-0.10	—	—	—	—	—	σ	14
	—	-0.04	-0.11	—	—	—	-0.12	—	σ^-	13
	—	-0.06	-0.08	—	—	—	—	—	σ	3
	—	—	—	—	—	-0.15	-0.03	—	σ	5
	-0.23	—	—	—	—	—	—	—	σ^+	16

EtO	—	—	—0.12	—	—	—	—	—	σ^-	13
	—	—0.02	—	—	—	—	—	—	σ	14
MeS	0.07	0.03	—	0.25	—	—	—	—	σ	1 ^e
	—	—	0.02	—	—	—	—	—	σ^-	13
NH ₂	0.09	0.12	0.30	—0.17	0.03	0.31	0.14	0.30	σ	1 ^f
	—	—	—	—	—0.06	—	—	—0.20	σ	5
NMe ₂	—	—	—	—	—	—	—	—0.06	σ	5
	—	—	—0.26	—	—	—	—	—	σ^-	13
CN	—	0.35	0.33	—	—	—	—	—	σ	3
SO ₃ ⁻	0.08	0.04	0.09	—0.40	0.05	0.13	0.06	0.08	σ^-	10 ^g
	0.40	—	—	—	—	—	0.38	0.39	σ^-	11 ^h
\geq N	0.35	—	—	0.27	—	—	—	—	σ	1 ⁱ
	0.62	—	—	—0.02	0.49	—	—	0.50	σ^-	11 ^j

* See Note added in proof, p. 247.

^d Taken from R. Riccardi and M. Bresesti, *Ann. Chim. (Rome)* **49**, 1891 (1959).

^e Taken from A. Albert and G. B. Barlin, *J. Chem. Soc.* **2384** (1959).

^f Taken from A. R. Osborn and K. Schofield, *J. Chem. Soc.* **4191** (1956).

^g Taken from A. Bryson, *Trans. Faraday Soc.* **47**, 522 (1951).

^h Taken from H. Zollinger and W. Büchler, *Helv. Chim. Acta* **33**, 2002 (1950).

ⁱ Taken from A. Albert, *J. Chem. Soc.* **1790** (1960).

^j A. Albert and J. N. Phillips, *J. Chem. Soc.* **1294** (1956).

excellent linear correlation observed as a scaling factor applicable to the ρ -value the pK correlation.



Illuminati *et al.*⁷⁹ have also investigated the methoxydechlorination of 4-substituted-2- and 2-substituted-4-chloroquinolines. The relation between the reaction site, the 2- or 4-position, and the substituent in the 4- or 2-position, respectively, is always *meta*. The authors found the two reaction series well correlated with one another, but diverging quite seriously from the Hammett correlation. They concluded that mesomerically electron-donating substituents, because of the importance of resonance structures like **12** and **13**, are more deactivating than expected, while electron-withdrawing substituents, and even the methyl group, seem to follow normal σ correlation.

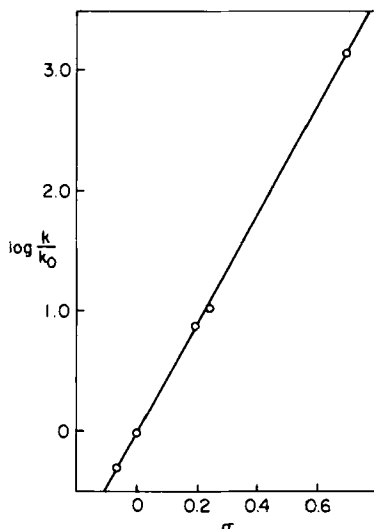


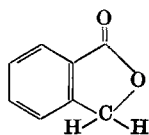
FIG. 6. The rates of methoxydechlorination of substituted 2-chloroquinoxalines in methanol at 5°; cf. ref. 80.

⁷⁹ M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron*, **19**, 345 (1963).

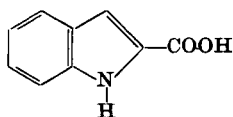
Illuminati *et al.*⁸⁰ have also investigated the methoxydechlorination of a series of 2-chloroquinoxalines. Since ρ -values for the 2- and 4-chloroquinolines differ and since no ρ -values for 3-chloro compounds are available, direct calculation of bicyclic σ -constants was not possible from these data. Figure 6 shows a plot of these data against the available σ -values obtained from the methoxydechlorination of the 2-chloroquinolines (cf. Table VII), which is seen to be excellently linear, with a ρ -value of 4.55, somewhere between the values for the 2- and 4-chloroquinoline series. From this ρ -value, σ -values for groups which were not otherwise available have been calculated and are included in Table VII.

B. FUSED FIVE- AND SIX-MEMBERED RINGS

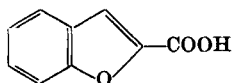
Finally, the Hammett equation has been applied in a few instances to heterocycles of the indole-benzofuran type. The double ρ method of Eq. (3) was first designed for this type of system and was here applied. When this approach was originally proposed,⁷² the only truly heterocyclic system to which it was applied was the substituted phthalids **14**,⁸¹ and pertinent data on the hydrolysis of these compounds are included in Table IX.



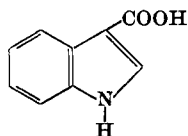
[14]



[15]



[16]



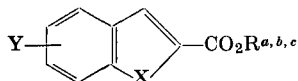
[17]

⁸⁰ G. Bressan, A. Ciana, G. Illuminati, and G. Marino, *Ric. Sci.* **33** (II-A), 533 (1963); G. Illuminati, P. Linda, G. Marino, and E. Zinato, *Ric. Sci.* **33** (II-A), 535 (1963); G. Illuminati and G. Marino, *Atti Acad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **34**, 407 (1963).

⁸¹ J. Tirouflet, *Bull. Soc. Sci. Bretagne Spec.* **26**, 89 (1951); J. Vène, J. Tirouflet, and P. Carré, *Compt. Rend.* **234**, 2074 (1952); J. Vène, J. Tirouflet, and C. Pinel, *ibid.* **236**, 1675 (1953).

This concept has also been applied to the acid-base equilibria of indole-2-carboxylic acids (**15**) and of coumarilic acids (**16**) and to the rates of saponification of their ethyl esters.⁸² The data were excellently

TABLE VIII
THE pK -VALUES AND THE HYDROLYSIS RATES OF



Y	X	pK	$k \times 10^3$, l. mole ⁻¹ sec ⁻¹
5-OMe	>NH	5.24	1.70
5-Me	>NH	5.21	1.77
H	>NH	5.28	2.62
5-Br	>NH	4.71	4.68
5-NO ₂	>NH	4.10	18.0
6-OMe	>NH	5.25	—
6-Me	>NH	5.29	1.61
6-Cl	>NH	5.14	4.72
5-OMe	>O	4.68	25.2
5-Me	>O	4.50	46.6
H	>O	4.35	81.0
5-Cl	>O	4.07	213.0
5-NO ₂	>O	3.55	1210.0
6-OMe	>O	4.34	34.0
6-Me	>O	4.63	—

^a The pK -values are determined in 50% ethanol at 25°, the ester hydrolyses in 85% ethanol at 35°.

^b R = H or CH₂CH₃.

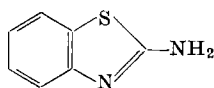
^c Cf. Y. Otsuji and H. H. Jaffé, Abstr. of Papers, 137th Meeting, Am. Chem. Soc., Cleveland, Ohio, April 1960, p. 76 O.

represented by the Hammet equation; however, the ideal of assessing the relative transmission of electronic effects through >NH and >O in this manner, by comparison of the various ρ -values, was not achieved satisfactorily. It seems likely, although not established, that hydrogen-bonding interactions between the carboxyl group and the heteroatom

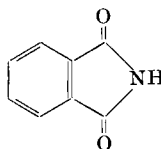
⁸² Y. Otsuji and H. H. Jaffé, Abstr. of Papers, 137th Meeting, Am. Chem. Soc., Cleveland, Ohio, April 1960, p. 76 O.

modify the simpler situation of the ester hydrolysis. The pertinent data are given in Tables VIII and IX.

A similar treatment of the indole-3-carboxylic acids⁸³ (17) led to the not too surprising conclusion that in these compounds substituent effects are transmitted to the reaction site predominantly through the direct linkage to the benzo ring, not by way of the longer path through the heteroatom. Quite analogous are the series of basicities of 2-aminobenzthiazoles (18),⁸⁴ the methoxydechlorination of 2-chlorobenzthiazoles,^{84a} and the oxidation of 2-methylmercaptobenzthiazoles to the sulfoxides.^{84b} The latter two series show very much smaller ρ -values for transmission through $>S$ than through $\geq N$ (cf. Table IX), and the uncertainties in the ρ -values are so large that this quantity is not different from zero. This suggests that the data do not provide any evidence for transmission of electronic effects through sulfur, and this conclusion may be verified by a comparison of the one-term Hammett equation for transmission through $\geq N$ with the two-term Eq. (3) as used in Table IX by analysis of variance. The method is outlined in the Appendix, and the result shows that no significant improvement results from use of Eq. (3) and, hence, that transmission through sulfur is not established.



[18]



[19]

Analogous, but slightly different, is the treatment of the acid-base equilibria⁸⁵ and the basic hydrolysis rates⁸⁶ of the phthalimids (19). In both of these cases, the two paths to the reaction site are equivalent, hence ρ_1 and ρ_2 of Eq. (3) are equal, and the equation reduces to:

$$\log(k/k^0) = (\sigma_m + \sigma_p)\rho. \quad (4)$$

The data for all these series are collected in Table IX.

⁸³ M. Melzer, *J. Org. Chem.* **27**, 496 (1962).

⁸⁴ G. Costa, *Ann. Chim. (Rome)* **43**, 585 (1953).

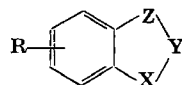
^{84a} P. E. Todesco and P. Vivarelli, *Gazz. Chim. Ital.* **92**, 1221 (1962).

^{84b} P. E. Todesco and P. Vivarelli, *Boll. Sci. Fac. Chim. Ind. Bologna* **20**, 129 (1962).

⁸⁵ C. Guérillot, *Compt. Rend.* **240**, 1107 (1955).

⁸⁶ J. Tirouflet and E. LeTrouit, *Compt. Rend.* **241**, 1053 (1955).

TABLE IX
REACTION CONSTANTS FOR THE SYSTEM



X	Z	Y	Reaction of Y	Solvent	Temp., °C	ρ_z^a	$s\rho_x^b$	ρ_z^c	$s\rho_z^d$	s^e	R^f	n^g	Ref.
>NH	>CH	$\text{>C-CO}_2\text{H}$	pK	50% EtOH	25	0.30	0.33	0.78	0.35	0.18	0.916	8	82
>NH	>CH	$\text{>C-CO}_2\text{Et}$	base hydrolysis of esters	85% EtOH	35	0.47	0.07	0.51	0.09	0.04	0.990	7	82
>O	>CH	$\text{>C-CO}_2\text{H}$	pK	50% EtOH	25	0.92	0.19	0.16	0.19	0.10	0.978	7	82
>O	>CH	$\text{>C-CO}_2\text{Et}$	base hydrolysis of esters	85% EtOH	35	1.03	0.13	0.70	0.13	0.07	0.997	6	82
>C=O	>C=O	>N-H	pK	H_2O	20	-0.87 ^a	0.04	—	—	0.07	0.996	6	85
>C=O	>C=O	>N-H	pK	H_2O	25	-0.94 ^a	0.03	—	—	0.05	0.998	6	85
>C=O	>C=O	>N-H	pK	H_2O	35	-1.06 ^a	0.04	—	—	0.08	0.997	6	85
>C=O	>C=O	>N-H	base hydrolysis	H_2O	35	0.73 ^a	0.04	—	—	0.06	0.997	4	86

$\begin{array}{c} \text{CH} \\ \diagup \quad \diagdown \\ \text{NH} \end{array}$	—	$\text{C}=\text{CO}_2\text{H}$	pK	50% EtOH	~26	-0.67 ⁱ	0.10	<i>j</i>	—	0.12	0.952	6	83
$\begin{array}{c} \text{CH} \\ \diagup \quad \diagdown \\ \text{NH} \end{array}$	—	$\text{C}=\text{CO}_2\text{H}$	pK	95% EtOH	~26	-1.28 ⁱ	0.23	<i>j</i>	—	0.13	0.966	5	83
$\text{N}=\text{S}$	S	$\text{C}=\text{NH}_2$	pK	5% EtOH	25	1.47	0.25	1.10	0.25	0.05	0.972	5	84
$\text{N}=\text{S}$	S	$\text{C}=\text{Cl}$	methoxydechlori- nation ^k	MeOH	25 35	1.96 1.91	0.33 0.21	0.71 0.58	0.58 0.23	0.47 0.19	0.956 0.992	8 8	84a 84a
$\text{N}=\text{S}$	S	$\text{C}=\text{SMe}$	oxidation by perbenzoic acid ^l	dioxane	25	-0.44	0.06	-0.09	0.06	0.05	0.983	9	84b

^a Reaction constant for the transmission of electrical effects through atom X to Y.

^b The reaction series in which the N group is treated as a substituent.

^c Reaction constant for the transmission of electrical effects through atom Z to Y.

^d Cf. footnote "b".

^e R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* 7317 (1959).

^f H. H. Jaffé, *Chem. Revs.* 53, 191 (1953).

^g A. Albert and G. B. Barlin, *J. Chem. Soc.* 2384 (1959).

^h Since X = Z, the reaction constant ρ_X is identical to ρ_Z .

ⁱ Calculated on the assumption that no transmission of electronic effects occurs through the indole nitrogen atom.

^j Assumes no transmission through this atom.

^k Since ρ_S is not significant, ρ_N for a one-term Hammett equation is 2.46 ± 0.35 at 25°, 2.32 ± 0.19 at 35°; $s = 0.49$ and 0.26 , $r = 0.943$ and 0.981 , respectively.

^l Since ρ_S is not significant, ρ_N for a one-term Hammett equation is -0.51 ± 0.08 , $s = 0.16$, $r = 0.976$.

The same data, including those involving substituents in the 3-position, which are in a vicinal relation to the "side-chain," have been treated by Guérillot using σ -values theoretically calculated for this reaction series and give an excellent correlation.¹⁰ This represents the first test of his theoretical treatment of the Hammett equation.

In the light of the application of the Hammett equation to five-membered heterocycles (see Section IV, B), one may attempt to apply the bicyclic substituent constants of the preceding section to the above data. For this purpose the heterocyclic atom is considered equivalent to $\text{CH}=\text{CH}$ to define the relative positions of the reaction site and side-chains. The reaction constants are available only for the two furan reaction series⁶⁸ — although an adjustment for the change in conditions has to be made by scaling the ρ -values in proportion to the corresponding ratios for the same reactions in benzenes. The substituent constants calculated in this manner are included in Table VI and are seen to fall well within the ranges given for the naphthalene and azanaphthalene reaction series.

VI. Tautomeric Equilibria

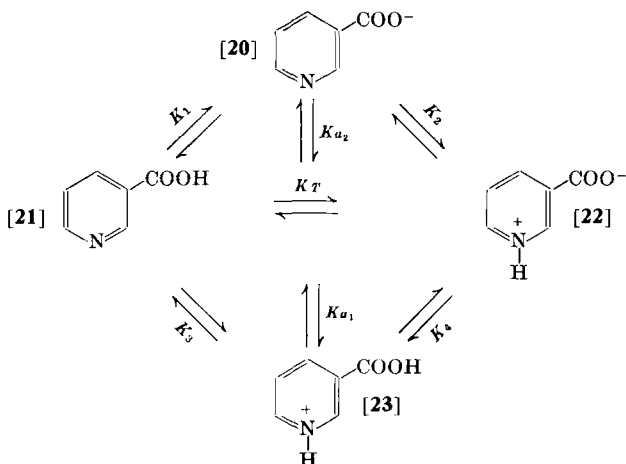
Once the concept that the Hammett equation may be applied to heterocyclic systems as well as to simple benzene derivatives is accepted the possibilities of its use are virtually unlimited. Curiously enough, not too many such applications seem to have been reported.

One interesting problem frequently recurring in heterocyclic chemistry, particularly with respect to nitrogen heterocycles, is tautomeric equilibria. Too many methods are available for the elucidation of equilibrium positions and tautomeric equilibrium constants (K_T) to adequately review the whole question here.⁸⁷ However, the Hammett equation provides one independent method⁴⁴; this method has the advantage that it can be used to predict the equilibrium position and to estimate the equilibrium constant, K_T , even in cases where the equilibrium position is so far to one side or the other that experimental determination of the concentration of the minor component is impossible. The entire method will be illustrated using nicotinic acid as an example but is, of course, completely general.

Free nicotinic acid can exist in neutral (21) and in zwitterion forms (22). On reaction with acid either form is converted into the same

⁸⁷ Cf. A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* **1**, 311 (1962).

conjugate acid (22), and on reaction with base both forms are converted into the same conjugate base (20); these reactions are summarized in the following equilibrium scheme. As indicated by the



arrows and the equilibrium constants, there are seven readily definable equilibria, however only three of the equilibria are independent. K_{a_1} and K_{a_2} , the experimentally observable first and second acid dissociation constants of the conjugate acid (23), are given by :

$$K_{a_1} = ([21] + [22]) \cdot [H^+] / [23] \quad (5)$$

$$K_{a_2} = [20] \cdot [H^+] / ([21] + [22]) \quad (6)$$

The tautomeric constant, K_T , is defined by :

$$K_T = [21] / [22] \quad (7)$$

The four ideal, experimentally inaccessible acid dissociation constants, K_1 , K_2 , K_3 , and K_4 , are given by :

$$K_1 = [20] \cdot [H^+] / [21] \quad (8)$$

$$K_2 = [20] \cdot [H^+] / [22] \quad (9)$$

$$K_3 = [21] \cdot [H^+] / [23] \quad (10)$$

$$K_4 = [22] \cdot [H^+] / [23] \quad (11)$$

Substitution of Eq. (7-11) into Eqs. (5) and (6) gives :

$$K_{a_1} = K_3(1 + K_T) / K_T \quad (12)$$

$$K_{a_1} = K_4(1 + K_T) \quad (13)$$

$$K_{a_2} = K_1 K_T / (1 + K_T) \quad (14)$$

$$K_{a_2} = K_2 / (1 + K_T) \quad (15)$$

The constants K_{a_1} and K_{a_2} are readily determinable experimentally. Eqs. (12–15) show that knowledge of any one of the constants K_1 to K_4 permits estimation of K_T . Even if only one experimental constant, K_{a_1} or K_{a_2} , is available, knowledge of K_3 or K_4 , or K_1 or K_2 , respectively, permits evaluation of K_T .

These constants, K_1 to K_4 , may be estimated by use of the Hammett equation. Estimation of K_1 and K_4 involves application of the methods outlined in Section II, A, i.e., application of substituent constants for $\geq N$ and $\geq N+H$ to the Hammett equation for the acid-base equilibria of benzoic acids. Estimation of K_2 and K_3 involves application of the method used in Section III, A, i.e., the ρ -value for the basicity of substituted pyridines, with σ -values for COOH and COO^- . Provided the necessary σ - and ρ -values are known, this procedure permits the calculation of four independent, or virtually independent, estimates of K_T . A check on the method is available from the relationships shown in Eq. (16) which is readily obtained by multiplication of Eq. (12) and (14) and of Eq. (13) and (15).

$$K_1 K_3 = K_{a_1} K_{a_2} = K_2 K_4 \quad (16)$$

Even when neither K_{a_1} nor K_{a_2} can be measured, K_T can be evaluated from K_1 and K_2 , or from K_3 and K_4 , since, by equating the right-hand sides of Eqs. (12) and (13), and of Eqs. (14) and (15), one obtains:

$$K_T = K_3/K_4 = K_1/K_2 \quad (17)$$

Thus, estimates of tautomeric equilibrium constants are available without any experimental data except the necessary σ - and ρ -values.

The methods outlined, of course, are readily applicable to a wide variety of substituted heterocycles like the carboxyl, hydroxy and mercapto derivatives of pyridines, pyridine 1-oxides, pyrroles, etc. The application to amines and to diaza compounds such as pyrimidine, where the two centers are basic, is obvious except that now **23** takes the role of the neutral compound, **21** and **22** the roles of the tautomeric first conjugate bases, and **20** the role of the second conjugate base. Extensions to molecules with more than two acidic or basic centers, such as aminonicotinic acid, pyrimidinecarboxylic acids, etc., are obvious although they tend to become algebraically cumbersome, involving (for three centers) three measurable K_a 's, four K_T 's, and fifteen ideal dissociation constants (K_i), a total of twenty-two constants of which seven are independent.

Another problem which frequently arises when the Hammett

equation is applied to potentially tautomeric systems concerns the effect of the tautomeric equilibrium on the applicability of the Hammett equation. Let us assume a molecule (which may be an ion, such as nicotinic acid cation) with two dissociable hydrogen atoms at nonequivalent sites, and let us further assume that we wish to express the effect of substituents on the equilibria for the two acid-base reactions in terms of the Hammett equation. An example in which such a treatment might have a reasonable chance of success is the 5-substituted nicotinic acids, but unfortunately no data are available. The equilibrium scheme is that shown on page 257 involving structures **20–23**, except that the substituents must be added to the 5-position. Then, e.g.,

$$\log (K_1^R/K_1^0) = \sigma_m^R \rho_1 \quad (18)$$

and

$$\log (K_2^R/K_2^0) = \sigma_m^R \rho_2 \quad (19)$$

where K_1^R and K_2^R are the equilibrium constants for the reaction of the 5-R-substituted compound and K_1^0 and K_2^0 are those of the parent compound; σ_m -values are used since R is *meta* to either reaction site. ρ_1 and ρ_2 refer, respectively, to the reactions **21** \rightarrow **20** and **22** \rightarrow **20**.

But, from Eqs. (5), (8), and (9),

$$\frac{1}{K_{a_1}} = \frac{1}{K_1} + \frac{1}{K_2} \quad (20)$$

This shows that the assumption made in Eqs. (18) and (19), i.e., that the Hammett equation is separately applicable to the component reactions, does not imply linearity of a plot of K_{a_1} vs. σ . The assumption of the applicability of the Hammett equation to the component series seems undeniable since these reactions are extremely closely related to series which follow the Hammett equation very well. This assumption also implies

$$\log (K_T^R/K_T^0) = \log \left[\frac{K_1^R}{K_1^0} \frac{K_2^0}{K_2^R} \right] = \sigma_M^R \rho_2 / \rho_1 \quad (21)$$

Again, examination of Eqs. (12–15) shows that K_{a_1} and K_{a_2} *cannot* be expected to be linear in σ , *unless* (a) K_T is substantially constant (independent of substituents) so that, according to Eq. (21), $\rho_1 = \rho_2$; (b) K_T is so large that 1.0 is negligible with respect to K_T and by Eqs. (12) and (14), respectively, $K_{a_1} = K_3$, $K_{a_2} = K_1$; or (c) K_T is so small that it may be neglected with respect to 1.0, and Eqs. (13) and (14) give $K_{a_1} = K_4$, $K_{a_2} = K_2$.

TABLE X
ANALYSIS OF VARIANCE

Line number	Source	Degrees of freedom ^a	Sum of squares	Mean square ^b	Variance Ratio, ^c F	Calculation of sum of squares ^d
1.	Total ^e	8	0.51869	—	—	$\Sigma Y^2 - (\Sigma Y)^2/n$
2.	Due to single regression	1	0.49373	0.49373	170**	$\rho \cdot \Sigma \sigma y$
3.	Due to double regression [Eq. (1)]	2	0.50131	0.25065	86**	$\rho_N \cdot \Sigma \sigma_N y + \rho_S \cdot \Sigma s y$
4.	Improvement	1	0.00758	0.00758	2.6 NS	line 3 — line 2
5.	Deviations from single regressions	7	0.02496	0.00357	1.2 NS	line 1 — line 2
6.	Deviations from double regressions	6	0.01738	0.00290	—	line 1 — line 3

^a For total, the number of compounds minus one, $n - 1$. For regressions, one per parameter (slope) calculated. For lines 4–6, calculated according to last column.

^b Sum of squares/degrees of freedom.

^c One asterisk indicates significance at 95%, two asterisks at 99% level. NS, not significant at 95% level. Calculated by dividing mean square of line by mean square for error; in this case deviations from double regression are used as an estimate of error. Significance determined from tables; cf., e.g., G. W. Snedecor, "Statistical Methods," 4th Edn. Iowa State College Press, Ames, 1946.

^d The formula by which the sum of squares is calculated. Y are the raw $\log k$, y the deviation of $\log k$ from their mean; σ_N and ρ_N the σ and ρ relative to transmission through nitrogen, etc. cf. the appendix of ref. 3.

^e The total sum of squares of deviation of $\log k$ from their mean.

These considerations show that caution must be exercised in applying of the Hammett equation to systems which are known to involve tautomeric equilibria, e.g. the pyridinecarboxylic acids or γ -hydroxypyridines. If in such systems the experimental pK_a -values are linear in σ , there is at least a strong suggestion that K_T is insensitive to the nature of the substituents. Some applications of these ideas in the azobenzene series have proved of considerable interest.⁸⁸

VII. Appendix: Analysis of Variance

One often wishes to determine if, in a least squares treatment, addition of a new parameter will improve *significantly* the fit of the data. This is readily achieved by analysis of variance.⁸⁹ Since this technique is little known, it will be briefly outlined here.

Let us take as an example some of the reaction series listed in Table IX, e.g. the oxidation of the 2-methylmercaptobenzothiazoles. The calculations are summarized in Table X, which is self-explanatory. In these calculations the deviations from regression were used as measure of error, but, when duplicate determinations are available, additional degrees of freedom for replication are obtainable, and should be used as measure of error.

⁸⁸ Ref. 44; see also H. H. Jaffé and R. W. Gardner, *J. Am. Chem. Soc.* **80**, 319 (1958); S. J. Yeh and H. H. Jaffé, *ibid.* **81**, 3279, 3283 (1959); J. H. Collins and H. H. Jaffé, *ibid.* **84**, 4708 (1962); Ref. 20, Chapter XX.

⁸⁹ H. H. Jaffé, *J. Org. Chem.* **23**, 874 (1958).

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1,2,3,4-Thiatriazoles

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I. Introduction

By reaction of thiosemicarbazide or its 4-alkyl derivatives with nitrous acid Freund and co-workers^{1, 2} in 1896 prepared compounds which were formulated as amino or alkylamino derivatives of the ring system 1,2,3,4-thiatriazole (**1**). Oliveri-Mandalà,³ however, argued that these compounds are actually thioazides (**2**), and this view seems to have been generally accepted (e.g. in Beilstein's *Handbuch*) until

¹ M. Freund and A. Schander, *Ber.* **29**, 2500 (1896).

² M. Freund and H. P. Schwarz, *Ber.* **29**, 2491 (1896).

³ E. Oliveri-Mandalà, *Gazz. Chim. Ital.* **44** I, 670 (1914).

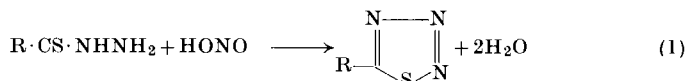
tives is limited by the fact that substitution can only take place in the 5-position; nevertheless, examples of several types of compounds—aldehydes, carboxylic acids, nitriles, sulfonic acids, etc.—are still missing.

Attempts in this laboratory to prepare the analogous 1,2,3,4-selenatriazoles have so far been unsuccessful. Acyl azides show no tendency to cyclize to 1,2,3,4-oxatriazoles.^{13, 14, 15}

II. Synthesis and Chemical Properties of 1,2,3,4-Thiatriazoles

A. SYNTHESIS

(1) The most general route to 1,2,3,4-thiatriazoles involves treatment of a thiohydrazide with nitrous acid [Eq. (1)]. Thus, 5-amino-



1,2,3,4-thiatriazole and its *N*-monoalkyl and *N,N*-dialkyl derivatives are obtained from thiosemicarbazide,^{1, 4} 4-alkylthiosemicarbazides,^{2, 6} and 4,4-dialkylthiosemicarbazides,^{6, 16} respectively. From 4-arylthiosemicarbazides Freund and Hempel¹⁷ obtained instead two isomers which were formulated as 5-mercaptotetrazoles and tetrazolinethiones. However, Lieber and Ramachandran¹⁸ have shown that the initial products are 5-arylamino-1,2,3,4-thiatriazoles, which on treatment with strong base rearrange to 5-mercaptotetrazoles (or tetrazolinethiones).

From thiohydrazides, $\text{R} \cdot \text{CS} \cdot \text{NHNH}_2$, in which R is an aromatic or a heterocyclic group, 1,2,3,4-thiatriazoles may in general be obtained in good yield by treatment with nitrous acid.^{8, 10, 11}

Xanthogenhydrazides, $\text{RO} \cdot \text{CS} \cdot \text{NHNH}_2$, give 5-alkoxy-1,2,3,4-thiatriazoles on treatment with nitrous acid,¹⁹ and dithiocarbazine esters, $\text{RS} \cdot \text{CS} \cdot \text{NHNH}_2$, give 5-alkylmercapto-1,2,3,4-thiatriazoles.²⁰

¹³ F. L. Scott, A. Koczarski, and J. Reillys, *Nature* **170**, 922 (1952).

¹⁴ E. Lieber and E. Oftedahl, *J. Org. Chem.* **24**, 1014 (1959).

¹⁵ K. A. Jensen, A. Holm, and S. Rachlin, *Acta Chem. Scand.*, in press.

¹⁶ V. Ya. Kazakov and I. Ya. Postovskii, *Dokl. Akad. NaukSSSR* **134**, 824 (1960).

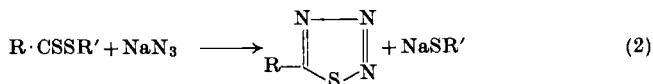
¹⁷ M. Freund and H. Hempel, *Ber.* **28**, 74 (1895).

¹⁸ E. Lieber and J. Ramachandran, *Can. J. Chem.* **37**, 101 (1959).

¹⁹ K. A. Jensen, A. Holm, and B. Thorkilsen, *Acta Chem. Scand.*, **18**, 825 (1964).

²⁰ E. Lieber, E. Oftedahl, S. Grenda, and R. D. Hites, *Chem. Ind. (London)* 893 (1958).

(2) Esters of dithioacids often give 1,2,3,4-thiatriazoles in good yield on treatment with sodium azide [Eq. (2)]; however, this method is not as general as method 1. Dithiocarbamic and xanthic acids and

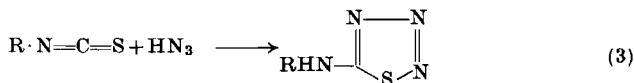


their esters do not react with sodium azide,¹⁹ nor could 1,2,3,4-thiatriazoles be obtained from carboxymethyl dithioesters, $\text{R} \cdot \text{CSSCH}_2\text{COOH}$, when R was alkyl, pyreryl, or indolyl.⁸ When R was aryl, furyl, or thienyl the dithioester reacted readily in most cases (exceptions: R = *o*- or *p*-hydroxyphenyl, α -naphthyl).

These reactions are preferably carried out with the carboxymethyl dithioesters, because these have the advantage of being soluble in aqueous sodium hydroxide. It has, however, been shown that the methyl esters, $\text{R} \cdot \text{CSSCH}_3$, react in the same way.⁸ Free dithiobenzoic acid reacted very slowly with sodium azide to give 5-phenyl-1,2,3,4-thiatriazole.⁹ Esters of monothioacids, $\text{R} \cdot \text{CSOCH}_3$, do not react with sodium azide. Bacchetti and Alemagna⁹ have, however, obtained 5-phenyl-1,2,3,4-thiatriazole from thiobenzoyl chloride, $\text{C}_6\text{H}_5\text{CSCl}$, and sodium azide. Chlorodifluorothioacetyl fluoride is converted into chlorodifluoroacetonitrile by heating with sodium azide, probably *via* a thiatriazole intermediate.²¹

Related reactions are those of sodium azide with carbon disulfide to give 5-mercapto-1,2,3,4-thiatriazole (see Section IV) and with thio-carbonyl chloride to give 5-chloro-1,2,3,4-thiatriazole.²²

(3) Isothiocyanates react with hydrogen azide to give 5-alkyl- (or -aryl-) aminothiatriazoles^{2, 6, 18, 23, 24, 25} [Eq. (3)]. This reaction is of



considerable theoretical interest, but as a preparative method the reaction of thiosemicarbazides with nitrous acid is more convenient and gives better yields.

²¹ N. N. Yarovenko, S. P. Motornyi, L. I. Kirenskaya, and A. S. Vasil'eva, *Zh. Obshch. Khim.* **27**, 2243 (1957).

²² E. Lieber, C. B. Lawyer, and J. P. Trivedi, *J. Org. Chem.* **26**, 1644 (1961).

²³ E. Oliveri-Mandalà, *Gazz. Chim. Ital.* **43 I**, 304 (1913).

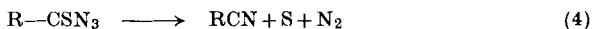
²⁴ E. Oliveri-Mandalà, *Gazz. Chim. Ital.* **51 II**, 195 (1921).

²⁵ E. Lieber and J. Ramachandran, *Chem. Ind. (London)* 461 (1958).

(4) From 5-chloro-1,2,3,4-thiatriazole and secondary amines Lieber *et al.*²² have prepared some 5-disubstituted-amino-1,2,3,4-thiatriazoles. It seems possible that several other types of compounds could be prepared from 5-chlorothiatriazole, which, however, is very unstable (explosive).

B. CHEMICAL PROPERTIES

The 1,2,3,4-thiatriazoles are unstable. They decompose on heating—in some cases even at room temperature—and in many cases they melt with detonation. Accordingly the N₃-group has not been stabilized much by ring closure. The compounds behave in this respect similarly to azides and this fact doubtlessly delayed the recognition of their true nature. On heating with a solvent the thermal decomposition of 5-aryl-1,2,3,4-thiatriazoles proceeds according to Eq. (4). By the photochemical decomposition small amounts of the isothiocyanate, RNCS, are formed in addition to the nitrile.^{10, 26}



An analogous decomposition of 5-amino-1,2,3,4-thiatriazole or 5-alkylamino-1,2,3,4-thiatriazoles gives cyanamide or an alkylcyanamide.^{1, 2}

Similar decomposition of alkylthio- and alkoxy-thiatriazoles should yield thiocyanates and cyanates, but they may rearrange to the *iso*-compounds and polymerize (see Sections IV, D and V).

III. 1,2,3,4-Thiatriazoles Substituted with C-Radicals

Thiatriazoles with an aromatic or heteroaromatic group in the 5-position (Table I) may in general be prepared by treatment of the corresponding thiohydrazide with nitrous acid or—in most cases—by the reaction of dithioesters with sodium azide. In no case could thiatriazoles with aliphatic substituents be isolated. The only known aliphatic thiohydrazide, thiopivalic hydrazide, gave an oil on reaction with nitrous acid, and this is probably the 5-*tert*-butyl-1,2,3,4-thiatriazole; it was, however, very unstable and decomposed in a few minutes at 0° C with nitrogen evolution and formation of sulfur.⁸ Esters or sodium salts of aliphatic dithioacids did not react with sodium azide.⁸ Cyclohexanethiocarboxhydrazide also gave an

²⁶ W. Kirmse, *Angew. Chem.* **71**, 381 (1959).

TABLE I*
 THIATRIAZOLES SUBSTITUTED WITH C-RADICALS

5-Substituent	Melting point, °C	References
<i>tert</i> -Butyl ^a	oil	8
Cyclohexyl ^a	oil	11
Benzyl	2	10
β -Phenylethyl ^a	oil	8
Phenyl	95-96	8, 9, 10, 11, 28
<i>o</i> -Tolyl	45-46	8
<i>p</i> -Tolyl	97-98	8, 28
<i>p</i> -Hydroxyphenyl	152-153	8, 28
<i>o</i> -Methoxyphenyl	104-105	8
<i>p</i> -Methoxyphenyl	103-104	8, 11, 28
<i>m</i> -Chlorophenyl	83-85	8
<i>p</i> -Chlorophenyl	101-102	8, 11, 28
<i>m</i> -Nitrophenyl	95-97	8
<i>p</i> -Nitrophenyl	130	10
<i>p</i> -Dimethylamino	168-171	28
<i>p</i> -Acetamidophenyl	141-142	8
α -Naphthyl	47-48	8, 10
β -Naphthyl	96-97	8, 10
2-Furyl	63-64	8
2-Thienyl	100-102	8
2-Pyrryl	130-131	8
3-Indolyl	135-136	8
4-(3-Methylpyrazol-5-onyl) ^b	140	27
4-(3-Methyl-1-phenylpyrazol-5-onyl) ^b	120-125	27

* See Notes Added in Proof, p. 284.

^a Unstable, not isolated in a pure state.

^b Formulated as thioazides in reference 27 but shown in this laboratory to be thiatriazoles.

unstable oil on treatment with nitrous acid.¹¹ It seems that 5-aralkyl-thiatriazoles are almost as unstable as the alkyl derivatives. With nitrous acid phenylthioacethydrazide and β -phenylthiopropionic hydrazide give oily products which decompose rapidly.⁸ Kirmse,¹⁰ however, succeeded in obtaining 5-benzyl-1,2,3,4-thiatriazole in a crystalline state (m.p. 2° C) from phenylthioacethydrazide and nitrous acid.

The 5-arylthiatriazoles, on the other hand, are as a rule quite stable, although they decompose on melting with the formation of nitrogen,

²⁷ P. Papini and M. Ridi, *Gazz. Chim. Ital.* **89**, 526 (1959).

²⁸ E. Lieber, M.S. Dept. Com., Office Tech. Serv., P.B. Rept. 148532 (1960); E. Lieber, C. N. R. Rao, and R. C. Orlowski, *Can. J. Chem.* **41**, 926 (1963).

sulfur, and a nitrile. 5-Phenylthiatriazole is extremely stable towards oxidizing agents, even chlorine, nitric acid, and peroxides. It has very weak basic properties, dissolving in concentrated hydrochloric or nitric acid. It does not react with methyl iodide and attempts by Smith and Kenny¹¹ to prepare a thiatriazolium salt by reaction of *N*¹-methylthiobenzhydrazide with nitrous acid resulted in cleavage of the *N*—*N* bond with formation of *N*-methylthiobenzamide. It was found to withstand both warm alcoholic alkali and Grignard reagents. However, reduction by lithium aluminum hydride occurred readily with formation of benzyl mercaptan.¹¹ Nitration of 5-phenylthiatriazole produced 5-(*p*-nitrophenyl)-thiatriazole.¹⁰

The low basicity and nucleophilicity, the inertness to oxidizing agents, and the deactivating influence on the benzene ring are all indicative of the pronounced aromatic character of the thiatriazole ring system and preclude the formulation of these compounds as thioazides. Also, in contrast to azides, the thiatriazoles are not reduced by hydrogen sulfide and do not have the thioacylating properties which would be expected from thioazides.⁸ Finally, an unambiguous proof of their constitution is the absence of the azide band in the 2100–2200 cm^{-1} region of the infrared spectrum^{7, 29}; this is a strong band, the position of which is influenced very little by the rest of the molecule.^{14, 30, 31}

IV. 1,2,3,4-Thiatriazole-5-thiol and Its Derivatives

A. THE THIOL

Compound **3** is one of the most thoroughly investigated thiatriazoles, but was originally supposed to have the structure of azidodithiocarbonic acid, $\text{N}_3\text{—CSSH}$.³² It is a fairly strong acid and its alkali metal and alkaline-earth metal salts are readily obtained by reaction of water-soluble azides with carbon disulfide at 40° C. This reaction was discovered by Sommer,³² who isolated and analyzed the sodium salt ($\text{NaSCSN}_3 \cdot 4\text{H}_2\text{O}$) and the barium salt ($\text{Ba(SCSN}_3)_2 \cdot 5\text{H}_2\text{O}$).

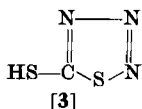
²⁹ E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.* **36**, 801 (1958).

³⁰ E. Lieber, C. N. R. Rao, T. S. Chao, and C. W. W. Hoffman, *Anal. Chem.* **29**, 916 (1957).

³¹ E. Lieber, D. R. Levering, and L. Patterson, *Anal. Chem.* **23**, 1594 (1951).

³² F. Sommer, *Ber.* **48**, 1833 (1915).

Detailed directions for the preparation of the sodium salt are given by Smith.³³ Sommer also made many qualitative observations on the properties of other salts and of the acid itself and its oxidation product, a disulfide. These observations were put on a firmer base by the extensive investigations of Browne *et al.*³⁴⁻⁴⁹ (see also references 50 and 51).



When Sommer tried to prepare the potassium salt of **3** the crystalline product obtained exploded with violence as he spread it upon a porous plate. The potassium salt was, however, isolated and analyzed by Browne and Hoel.³⁵ It is anhydrous but very soluble in water. Several other salts have been prepared.^{42, 43, 47, 49, 52} The slightly soluble heavy-metal salts are very sensitive to shock and may explode violently even under water.⁴⁷

³³ G. B. L. Smith, *Inorg. Syn.* **I**, 82 (1939).

³⁴ A. W. Browne and A. B. Hoel, *J. Am. Chem. Soc.* **44**, 2106 (1922).

³⁵ A. W. Browne and A. B. Hoel, *J. Am. Chem. Soc.* **44**, 2315 (1922).

³⁶ A. J. Currier and A. W. Browne, *J. Am. Chem. Soc.* **44**, 2849 (1922).

³⁷ A. W. Browne, A. B. Hoel, G. B. L. Smith, and F. H. Swezey, *J. Am. Chem. Soc.* **45**, 2541 (1923).

³⁸ G. B. L. Smith, F. Wilcoxon, and A. W. Browne, *J. Am. Chem. Soc.* **45**, 2604 (1923).

³⁹ F. Wilcoxon, A. E. McKinney, and A. W. Browne, *J. Am. Chem. Soc.* **47**, 1916 (1925).

⁴⁰ A. W. Browne and G. B. L. Smith, *J. Am. Chem. Soc.* **47**, 2698 (1925).

⁴¹ A. W. Browne and R. S. von Hazmburg, *J. Am. Chem. Soc.* **48**, 2383 (1926).

⁴² A. W. Browne and L. F. Audrieth, *J. Am. Chem. Soc.* **49**, 917 (1927).

⁴³ L. F. Audrieth, G. B. L. Smith, and A. W. Browne, *J. Am. Chem. Soc.* **49**, 2129 (1927).

⁴⁴ W. H. Gardner and A. W. Browne, *J. Am. Chem. Soc.* **49**, 2759 (1927).

⁴⁵ L. F. Audrieth, J. R. Johnson, and A. W. Browne, *J. Am. Chem. Soc.* **52**, 1928 (1930).

⁴⁶ L. F. Audrieth and A. W. Browne, *J. Am. Chem. Soc.* **52**, 2799 (1930).

⁴⁷ G. B. L. Smith, P. Warttman, and A. W. Browne, *J. Am. Chem. Soc.* **52**, 2806 (1930).

⁴⁸ G. B. L. Smith, F. P. Gross, Jr., G. H. Brandes, and A. W. Browne, *J. Am. Chem. Soc.* **56**, 1116 (1934).

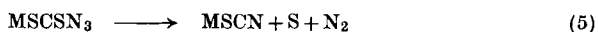
⁴⁹ J. Craik, K. H. Berger, and A. W. Browne, *J. Am. Chem. Soc.* **56**, 2380 (1934).

⁵⁰ R. Ullman and G. B. L. Smith, *J. Am. Chem. Soc.* **68**, 1479 (1946).

⁵¹ L. F. Audrieth, *Chem. Rev.* **15**, 196 (1934).

⁵² E. Lieber, E. Oftedahl, and C. N. R. Rao, *J. Org. Chem.* **28**, 194 (1963); E. N. Oftedahl, M.S. Thesis, De Paul University, Chicago, Ill., 1960.

Slow thermal decomposition of the alkali metal salts of **3** takes place quantitatively in accordance with Eq. (5),³⁵ where M represents an



alkali metal. Aqueous solutions of the soluble salts are quite stable at temperatures below 10° C, but at somewhat higher temperatures the solutions become turbid due to the liberation of sulfur. At the same time thiocyanate ions are formed.

The free acid, 1,2,3,4-thiatriazole-5-thiol, may be prepared from hydrogen azide and carbon disulfide,⁵³ but the simplest way to obtain the acid is to treat a chilled solution of the sodium salt with concen-

TABLE II
1,2,3,4-THIATRIAZOLE-5-THIOL AND DERIVATIVES

5-Substituent in thiatriazole ring	Melting point, °C	References
Mercapto	50–65 (decompn.)	7, 32, 38, 40, 42, 43, 48, 49, 52, 54
Methylthio	34	7, 20, 45
Allylthio	very unstable	45
Benzylthio	66	45, 52
<i>p</i> -Nitrobenzylthio	100–102	52
Phenacylthio	89	52
<i>p</i> -Chlorophenacylthio	106–108	52
<i>p</i> -Phenylphenacylthio	98	52
Diphenylmethylthio	67	45, 52
Triphenylmethylthio	102–104 (decompn.), 91–92	45, 52
Benzoylthio	92–94 (decompn.)	7, 45, 52
<i>p</i> -Bromobenzoylthio	99–101 (decompn.)	45
Thiocyanato	84–85 (decompn.)	46, 52
Thiatriazolethio	explodes	32, 37, 39, 41, 44

trated hydrochloric acid.³⁸ The acid is then obtained as a white or slightly yellow precipitate, which is fairly soluble in water and readily soluble in various organic solvents. The ionization constant of this acid has been determined by Hantzsch and Bucerius⁵⁴ and by Browne

⁵³ E. Oliveri-Mandalà, *Gazz. Chim. Ital.* **52** II, 139 (1922).

⁵⁴ A. Hantzsch and W. Bucerius, *Ber.* **59**, 795 (1926).

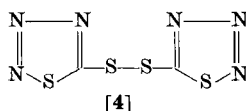
*et al.*⁴⁸ to be 2.8×10^{-2} and 2.14×10^{-2} , respectively. Accordingly it is a medium-strong acid. The acid is relatively stable below 10°C when protected from light, but it undergoes slow decomposition even at 0°C when exposed to daylight. It appears to melt between 50 and 65°C , but often explodes under this treatment. By the thermal decomposition sulfur, nitrogen, and (polymeric) thiocyanic acid are formed [Eq. (6)].



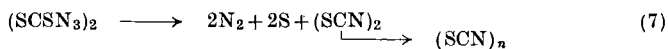
The salts of the thiol react with alkyl and acyl halides to form alkyl or acyl derivatives⁴⁵ (Table II). For a discussion of the constitution of these compounds see Section IV, D.

B. THE DISULFIDE

Both the free acid and its salts are transformed^{32, 37, 39, 44} into di-(1,2,3,4-thiatriazol-5-yl) disulfide (4) by various oxidizing agents [e.g. iodine, iron(III) chloride, hydrogen peroxide, permanganates, and nitric acid]. The disulfide is rather resistant to oxidation, but with an excess of such substances as concentrated nitric acid, hydrogen peroxide, or potassium permanganate the final products are sulfuric acid, carbon dioxide, and nitrogen (sometimes HCN).³⁷ No thiatriazole-5-sulfonic acid has been observed as an intermediate, but perhaps it has been missed.



The disulfide is a white crystalline solid; only three parts are soluble in 10,000 parts of water at 25°C , but it is appreciably soluble in many organic solvents. It is distinctly more sensitive to impact than is thiatriazole-5-thiol and may explode even under water. It undergoes gradual spontaneous and autocatalytic decomposition at room temperature with the liberation of nitrogen and the formation of a solid residue containing sulfur and polymeric thiocyanogen³⁷ [Eq. (7)]. Solutions of the disulfide in organic solvents undergo a similar decomposition with the deposition of yellow to dark orange solids.



There is no apparent reaction between the disulfide and dilute acids at room temperature, but with more concentrated acids liberation of nitrogen takes place and the solution becomes turbid due to the formation of sulfur.

The disulfide is dissolved by aqueous potassium hydroxide, yielding a greenish-yellow solution. At low temperatures no perceptible evolution of gas takes place. Since the disulfide in many respects behaves as a "pseudo-halogen," Brown *et al.*³⁷ have supposed that the reaction described by Eq. (8) takes place, i.e. a reaction analogous to the formation of halide and halite ions from a halogen and alkali.

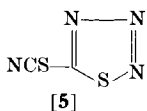


When the solution was acidified the disulfide again separated, but the solution also contained the thiol, and, therefore, these investigators supposed that the reaction had proceeded to form an analog not only of a halite but also of a halate [Eq. (9)]. The existence of the



compounds KOSCSN_3 and KO_3SCSN_3 has not been proved, but it would be of interest to try to isolate these compounds since they would in fact be salts of 1,2,3,4-thiatriazole-5-sulfenic acid and 1,2,3,4-thiatriazole-5-sulfonic acid.

The solid disulfide reacts explosively with chlorine or bromine. At low temperatures in certain non-aqueous solvents, e.g. chloroform, ClSCSN_3 and BrSCSN_3 are probably formed,⁴⁴ but the extreme instability of these compounds has precluded their exact analysis and description. However, the reaction between cyanogen bromide and the potassium salt of the thiol yields⁴⁶ the well-defined cyanide NCSCSN_3 ,



which is actually to be considered as 5-thiocyanato-1,2,3,4-thiatriazole (5). Unambiguous evidence for structure 5 derives from degradative and spectroscopic studies.⁵² On thermal degradation sulfur dicyanide, $\text{S}(\text{CN})_2$, is formed.

The disulfide is a moderately strong oxidant and liberates iodine on addition of an acidified iodide solution. As usual there is a reversible

equilibrium between the thiol and the disulfide. The standard oxidation potential of this reaction has been determined⁵⁰ to be 0.275 volt at 25° C. Accordingly, it is a somewhat weaker oxidant than iodine ($E^\circ = 0.53$ volt).

C. THE CS₂-CATALYZED IODINE-AZIDE REACTION

The disulfide has a special interest as the catalyst in the carbon disulfide-catalyzed iodine-azide reaction. No perceptible nitrogen evolution will take place in a solution containing iodine and azide ions without the presence of a catalyst. Thiosulfates, sulfides, and many other sulfur compounds act as catalysts.⁵⁵⁻⁵⁹ In 1922 Browne *et al.*^{34,36} found that carbon disulfide is a powerful catalyst in this reaction and showed that the reaction proceeds *via* "azidodithiocarbonic acid" and the corresponding disulfide. The reaction of the latter with azides may be expressed by Eq. (10). Accordingly, the disulfide was considered to be the true catalyst. Feigl and Chargaft,⁵⁸



in a later paper, considered carbon disulfide as the catalyst and postulated that it was regenerated during the reaction. It had, however, already been shown by Browne *et al.*³⁴ that this was not the case; no detectable amount of carbon disulfide was regenerated during the interaction of iodine and potassium azide in the presence of carbon disulfide, when once the disulfide had become fixed by combination with the azide. The extensive kinetic experiments by Hofman-Bang and co-workers⁶⁰⁻⁶³ confirmed the qualitative conclusions of Browne *et al.*³⁴ The reaction is a chain reaction which can be accounted for by the closed sequence of reactions summarized in Eqs. (11-14). In this sequence the first reaction [Eq. (11)] is the rate determining step and

⁵⁵ F. Raschig, *Ber.* **48**, 2088 (1915).

⁵⁶ F. Sommer and H. Pincas, *Ber.* **48**, 1963 (1915).

⁵⁷ F. Feigl, *Z. anal. Chem.* **74**, 369 (1928).

⁵⁸ F. Feigl and E. Chargaft, *Z. anal. Chem.* **74**, 376 (1928).

⁵⁹ F. Feigl, "Spot Tests," Vol. 1, pp. 265, 280, 294; Vol. 2, p. 301. Elsevier, Amsterdam, 1954.

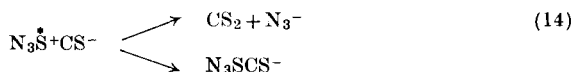
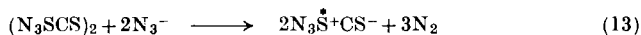
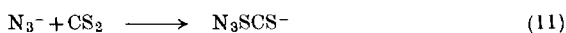
⁶⁰ N. Hofman-Bang and W. Szybalski, *Acta Chem. Scand.* **3**, 1418 (1949).

⁶¹ N. Hofman-Bang, *Acta Chem. Scand.* **4**, 856 (1950).

⁶² N. Hofman-Bang and B. Holten, *Acta Chem. Scand.* **5**, 333 (1951).

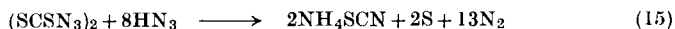
⁶³ N. Hofman-Bang, "The Iodine-Azide Reaction." C. A. Reitzels Forlag, Copenhagen, 1952.

all other reactions are very fast. The $\text{N}_3\ddot{\text{S}}^+\text{CS}^-$ ion is assumed to be an activated ion which can either emit energy and become an ordinary N_3SCS^- ion capable of reacting again with iodine, or decompose to carbon disulfide plus an azide ion. The probability of the latter decomposition determines the kinetic chain length, which was found by Hofman-Bang⁶³ to be 16–17 at room temperature. The hypothesis that iodine atoms play a role in this reaction⁶⁴ is not supported by experimental evidence.



According to Hofman-Bang⁶³ carbon sulfide selenide, CSSe , catalyzes the iodine-azide reaction but is at the same time decomposed with the formation of selenium. Experiments, in both this laboratory and that of Hofman-Bang have shown that carbon diselenide reacts with sodium azide (in aqueous or aqueous-alcoholic solution) with immediate precipitation of red selenium even at -20°C . If a selenatriazole is formed in this reaction it must be extremely unstable.

A different reaction takes place between an ethereal solution of the disulfide and hydrogen azide; this reaction proceeds according to Eq. (15).³⁹ Probably the principal step of this reaction is the spontaneous decomposition of the disulfide into nitrogen, sulfur, and



thiocyanogen. The latter reacts with hydrogen azide to form ammonium thiocyanate and nitrogen.

D. THE CONSTITUTION OF THE THIOL

Seel and Nógrádi⁶⁵ were probably the first to suspect that the formulation of the thiol as azidodithiocarbonic acid was incorrect. In a study of the reaction of nitrosyl chloride with azides they found that

⁶⁴ J. Weiss, *Trans. Faraday Soc.* **43**, 119 (1947).

⁶⁵ F. Seel and J. Nógrádi, *Z. Anorg. Allgem. Chem.* **264**, 311 (1951).

the thiol, unlike true azides, did not evolve nitrogen on treatment with nitrosyl chloride but was transformed into the disulfide. They concluded from this reaction that the supposed azidodithiocarbonic acid was actually thiatriazole-5-thiol. Another chemical reaction which is not in accordance with the formulation of this compound as an azide is its inertness towards hydrogen sulfide.

As mentioned in Section I, Lieber⁷ obtained the decisive proof of the thiatriazole formulation of the thiol from the study of its infrared spectrum and has recently shown⁵² that this conclusion applies generally to all derivatives of the thiol, including the heavy-metal salts. However, Lieber thinks⁷ that the parent compound is thiatriazoline-5-thione rather than thiatriazole-5-thiol. This seems very unlikely, because the compound has pronounced acid character and a thiatriazolinethione would not be expected to be a medium-strong acid. It should also be noted that the infrared spectrum, according to Lieber, exhibits absorption at 2533 cm^{-1} , which is only a little lower than the normal position of an S—H band. For unknown reasons Lieber *et al.*⁷ assign this band to an N—H vibration. We think that the fact that this compound is a medium-strong acid is sufficient evidence that it is a thiol. For the same reason we think Lieber's formulation of tetrazole-5-thiols as tetrazolinethiones¹⁸ is incorrect. It should be remembered that the infrared spectra were obtained on solid material and therefore are not spectra of isolated molecules but spectra of molecule-aggregates. Since these compounds are rather strong acids, the aggregates will have the character of a pseudo-ionic structure with weakened S—H vibrations and perhaps the appearance of N—H vibrations. The fact that the S—H band is not apparent, therefore, in our opinion, is not decisive evidence that the compounds are not thiols. In the anions, of course, there must be considerable delocalization of the negative charge.

Lieber *et al.*²⁰ have discussed whether the compound obtained from the sodium salt of the thiol and methyl iodide is an *N*- or an *S*-derivative and have proved that it is the *S*-derivative by syntheses of this compound from methyl dithiocarbazinate ($\text{CH}_3\text{S—CS—NH—NH}_2$) and nitrous acid. The acyl derivatives are, however, formulated as *N*-acylthiatriazoline-5-thiones, because they are decomposed to form acylisothiocyanates. Lieber *et al.*^{66, 67} have shown that thiocyanates

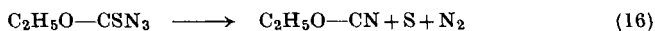
⁶⁶ E. Lieber and E. N. Oftedahl, *Chem. Ind. (London)* 1303 (1960).

⁶⁷ E. Lieber, C. N. R. Rao, and J. Ramachandran, *Spectrochim. Acta* **13**, 296 (1959).

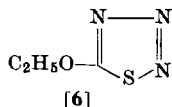
and isothiocyanates may conveniently be distinguished by means of their infrared spectra and think that a differentiation of *N*- and *S*-substituted derivatives of the thiol can be obtained from degradation experiments, but this seems unlikely. During the degradation a rearrangement may take place with the formation of the most stable isomer and it is therefore not surprising that the acyl derivatives give the isothiocyanates, since acylthiocyanates are so unstable that they cannot be isolated. The same applies to the diphenylmethyl and triphenylmethyl derivatives, which Lieber *et al.*⁵² formulate as *N*-derivatives. The allyl derivative, which must be analogous to the *S*-methyl derivative, also gives allylisothiocyanate,⁴⁵ in accordance with the easy transformation of allylthiocyanate into isothiocyanate. Awaiting conclusive evidence for the structure of these compounds, we have listed all of them as *S*-derivatives in Table II.

V. 5-Alkoxy-1,2,3,4-thiatriazoles

Sodium azide does not react with carbonylsulfide to form 5-hydroxy-1,2,3,4-thiatriazole, nor with carboxymethyl xanthates, $\text{RO} \cdot \text{CS} \cdot \text{SCH}_2\text{COOH}$, to form 5-alkoxy-1,2,3,4-thiatriazoles.¹⁹ The latter, however, could be prepared from xanthogenhydrazides ($\text{RO} \cdot \text{CS} \cdot \text{NHNH}_2$) and nitrous acid.¹⁹ They are very unstable and may decompose explosively at room temperature; only the ethoxy compound (6) has been examined in detail. This is a solid which decomposes rapidly at room temperature and even at 0°C is transformed after some months into a mixture of sulfur and triethyl isocyanurate. In ethereal solution at 20°C the decomposition takes place according to Eq. (16)



and it has been possible to isolate the hitherto unknown ethyl cyanate, $\text{C}_2\text{H}_5\text{O}-\text{CN}$. This is slowly isomerized to ethyl isocyanate which may polymerize to triethyl isocyanurate. Under less controlled conditions these reactions proceed violently.



VI. 5-Substituted-amino-1,2,3,4-thiatriazoles

A. SYNTHESIS

As mentioned in Section I, the product obtained by Freund and Schander¹ in 1896 by the reaction of thiosemicarbazide with one

mole⁶⁸ of nitrous acid was shown by Lieber *et al.*⁴ to be 5-amino-1,2,3,4-thiatriazole and not thiocarbamoyl azide, since its infrared spectrum showed no absorption in the range characteristic of the azide group. From 4-alkylthiosemicarbazides and nitrous acid Freund and Schander¹ also prepared some 5-alkylamino-1,2,3,4-thiatriazoles, and Lieber

TABLE III*
5-SUBSTITUTED-AMINO-1,2,3,4-THIATRIAZOLES

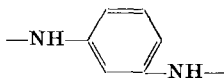
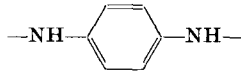
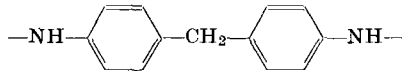
Substituents on amino group		Melting point, °C	References
R	R'		
H	H	128–130	1, 4, 5, 29, 71, 72
Methyl	H	96	2, 6, 29, 71, 72
Ethyl	H	66–67	2, 6, 29, 71
Propyl	H	58–59	73
Isopropyl	H	62–63	73
Butyl	H	40–41	6, 29, 71
Isobutyl	H	27–31	73
<i>sec</i> -Butyl	H	27–29	73
<i>tert</i> -Butyl	H	113–114	73
Heptyl	H	75–76	6, 29, 71
Allyl	H	53–54	2, 6, 29, 71
Ethoxycarbonylmethyl	H	69–69.5	73
Cyclohexyl	H	108–109	73
Benzyl	H	80–81	6, 29, 71
β -Phenylethyl	H	90–91	73
Phenyl	H	142–143	6, 17, 23, 29, 71
Diphenylmethyl	H	132–133	73
Triphenylmethyl	H	167–168	73
<i>o</i> -Tolyl	H	114–115	6, 29, 71
<i>p</i> -Tolyl	H	142–144	3, 6, 29, 71
<i>o</i> -Methoxyphenyl	H	89–90	6, 29, 71
<i>p</i> -Methoxyphenyl	H	136–137	6, 29, 71
<i>p</i> -Fluorophenyl	H	127–128	18
<i>p</i> -Chlorophenyl	H	147–148	6, 29, 71
2,4-Dichlorophenyl	H	140	18
<i>p</i> -Nitrophenyl	H	152–153	18
<i>p</i> -Dimethylaminophenyl	H	140	18
Methyl	Methyl	49–51	6, 16, 22, 29, 71, 74
Methyl	Phenyl	56.5	69
Ethyl	Phenyl	148.5–149	69
Benzyl	Benzyl	89–90	69
Phenyl	Phenyl	146–147	73

* See Notes Added in Proof, p. 284.

⁶⁸ R. H. Sahasrabudhey and H. Krall, *J. Indian Chem. Soc.* **13**, 226 (1941).

et al.^{6,18} have prepared several others. Some 4,4-dialkyl-1,2,3,4-thiatriazoles have been prepared in the same way.^{6,16} However, in some cases the disubstituted aminothiatriazole could not be obtained from the corresponding thiosemicarbazide but was prepared from the corresponding thiocarbamoyl chloride and sodium azide.⁶⁹ A few mono- and di-substituted-aminothiatriazoles have also been prepared 5-chloro-1,2,3,4-thiatriazole and an amine.²²

TABLE IV
VARIOUS 5-SUBSTITUTED-THIATRIAZOLES

5-Substituent	Melting point, °C	References
Chloro	explodes	22
Ethoxy	44–45 (decompn.)	19
Piperidino	28–29	16, 74
Morpholino	114–115	16, 74
	162	70
	180	70
	148	70

From 4-phenylthiosemicarbazide Freund and Hempel¹⁷ obtained a product to which they assigned the structure of a tetrazolinethione. When heated in alkaline solution it was isomerized to a compound which, on the basis of adequate chemical evidence, was considered to be 5-mercapto-1-phenyltetrazole. According to Lieber and Ramachandran,¹⁸ however, the initial product is 5-phenylamino-1,2,3,4-thiatriazole. Lieber and Slutkin⁷⁰ have also converted some di(thiosemi-

⁶⁹ C. B. Lawyer, M.S. Thesis, De Paul University, Chicago, Ill., 1960; E. Lieber, C. N. R. Rao, C. B. Lawyer, and J. P. Trivedi, *Can. J. Chem.* **41**, 1643 (1963).

⁷⁰ E. Lieber and R. Slutkin, *J. Org. Chem.* **27**, 2214 (1962).

⁷¹ E. Lieber, C. N. Pillai, E. Oftedahl, and R. D. Hites, *Inorg. Syn.* **VI**, 42 (1960).

⁷² M. Kuhn and R. Mecke, *Z. anal. Chem.* **181**, 487 (1961).

⁷³ K. A. Jensen, A. Holm, and C. T. Pedersen, *Acta Chem. Scand.*, **18**, 566 (1964).

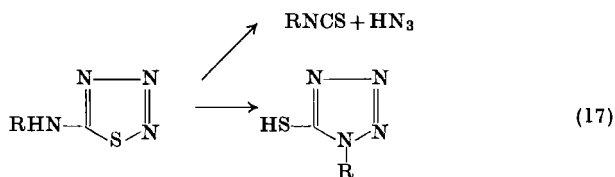
⁷⁴ British Patent 861,056 (Feb. 15, 1961); *Chem. Abstr.* **55**, 26551 (1961).

carbazides) into the corresponding thiatriazoles by treatment with nitrous acid.

Accordingly, 5-substituted-amino-1,2,3,4-thiatriazoles (Tables III and IV) are formed quite generally from 4-substituted-thiosemicarbazides. When the substituent is an aryl group these initial products are isomerized to 5-mercaptotetrazoles on treatment with alkali whereas this is not the case when the substituent is an alkyl group.

B. DECOMPOSITION OF 5-AMINO-1,2,3,4-THIATRIAZOLE AND ITS DERIVATIVES

The 5-alkylamino-1,2,3,4-thiatriazoles are cleaved by alkali into an azide ion and an isothiocyanate. The same reaction takes place to some extent also when the substituent is an aryl group, so that we have to deal with two competing reactions [Eq. (17)]. According to Lieber



*et al.*⁶ tetrazole formation is favored when R is an electronegative group, and further tetrazole formation appears to increase as the electronegativity of R increases. The yield of the tetrazole is, however, always low (24–37%), but since the tetrazoles are stable towards alkali the loss must be due to the competing reaction. This was shown actually to be the case by identification of phenylisothiocyanate, aniline, *s*-diphenylthiourea, and hydrazoic acid together with 5-mercapto-1-phenyltetrazole as the reaction products, when 5-phenylamino-1,2,3,4-thiatriazole was submitted to an alkaline steam degradation.

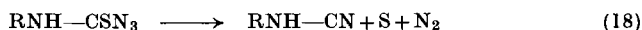
Lieber *et al.*^{6, 18} have advanced some hypotheses concerning the mechanism of these reactions. A discussion of these is, however, outside the scope of this review.

As shown by Oliveri-Mandalà^{3, 23, 24} and by Lieber *et al.*,⁶ 5-substituted-amino-1,2,3,4-thiatriazoles are also formed by reaction of isothiocyanates with hydrazoic acid. When sodium azide is used instead of the free acid the isomeric mercaptotetrazoles are formed.^{18, 75}

⁷⁵ R. Stollé, *J. Prakt. Chem.* **124**, 261 (1930); **133**, 60 (1932); *Ber.* **63**, 670 (1930).

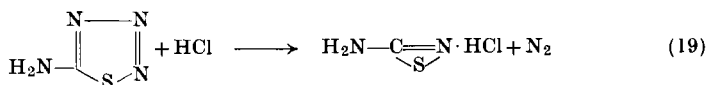
The thiatriazoles are recovered quantitatively and unchanged after treatment with hydrogen sulfide. This is convincing chemical evidence against the thioazide formulation.

Somewhat above their melting points the aminothiatriazoles decompose more or less violently. When they are heated in aqueous solution nitrogen and sulfur are formed together with a cyanamide (isolated by Freund and Schwarz² as the trimeric melamines) [Eq. (18)]. With the unsubstituted 5-aminothiatriazole the reaction



product is cyanamide, which was isolated by Freund and Schander¹ as dicyandiamide. The correctness of this result was questioned by Scott *et al.*,¹³ but it has been confirmed by Lieber *et al.*⁵ The weak base aniline acts in the same way as water. With an excess of a stronger base the same reaction takes place as with sodium hydroxide, i.e. the formation of azide and thiocyanic acid. Thus from the reaction of 5-aminothiatriazole with one mole of benzylamine Lieber and Pillai⁵ isolated benzylguanidine, the reaction product of cyanamide with benzylamine. However, with excess benzylamine the reaction products were benzylammonium azide, benzylthiourea, and dibenzylthiourea (formed from thiocyanic acid and benzylamine).

On treatment of 5-amino-1,2,3,4-thiatriazole with concentrated hydrochloric acid Freund and Schander¹ obtained a hydrochloride of a sulfur-containing substance which was thought to be a three-membered ring compound [cf. Eq. (19)]. The possibility that it might be a dimer with a six-membered ring was, however, left open.



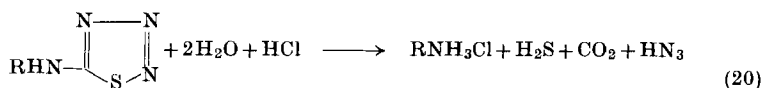
5-Alkylamino-1,2,3,4-thiatriazoles react in the same way as the unsubstituted compound. The compounds obtained have also been formulated as thiocynoamines, RNHNCS .⁷⁶

However, Sahasrabudhey⁷⁷ thinks that the compound formed from 5-amino-1,2,3,4-thiatriazole does not have the composition $\text{CSN}_2\text{H}_3\text{Cl}$, but $(\text{CSN}_2\text{H}_4\text{Cl})_2$, and is in fact the dihydrochloride of formamidine disulfide, the oxidation product of thiourea. This con-

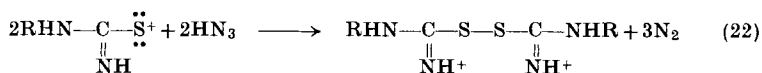
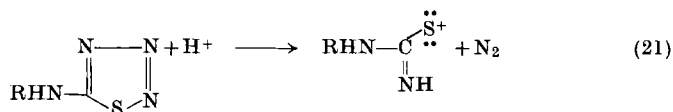
⁷⁶ P. A. S. Smith, *Org. Reactions* **III**, 362 (1946).

⁷⁷ R. H. Sahasrabudhey, *J. Indian Chem. Soc.* **27**, 524 (1950).

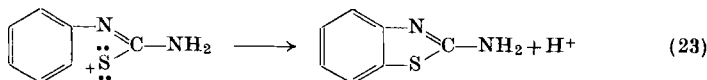
clusion was based on the identity of the melting points of four salts of Freund's compound with the melting points of the correspondingsalts of formamidine disulfide. Experiments⁷⁸ in this laboratory have shown that this formulation is correct, the infrared spectra of the degradation product of 5-amino-1,2,3,4-thiatriazole and formamidine disulfide dihydrochloride being identical. Moreover, it was found generally that the compounds formed from 5-alkylamino-1,2,3,4-thiatriazoles and hydrochloric acid are the corresponding alkyl-substituted formamidine disulfides. This result is rather surprising since it means that a reduction of the thiatriazole has taken place. At the same time about 50% of the thiatriazole is hydrolyzed with the formation of hydrogen sulfide, hydrazoic acid, and carbon dioxide. No sulfur or thiocyanic acid is formed in this reaction, which therefore takes place according to Eq. (20). A plausible explanation of the formation of the formamidine disulfide is then that hydrazoic acid functions as a reducing



agent (as it does in the iodine-azide reaction) and reduces the positive ion formed by the opening of the thiatriazole ring under the influence of the strong acid [Eqs. (21) and (22)]. When R = aryl the reaction



takes another course, and 2-aminobenzothiazoles^{12, 76} are formed. This is readily explained as an electrophilic attack of the initially formed positive ion on the aromatic nucleus [Eq. (23)].



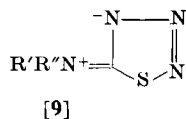
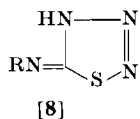
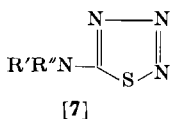
⁷⁸ K. A. Jensen and A. Holm, *Acta Chem. Scand.*, **18**, 570 (1964).

C. THE CONSTITUTION OF 5-AMINO-1,2,3,4-THIATRIAZOLE AND ITS DERIVATIVES

These compounds exhibit no infrared absorption in the 2100–2200 cm^{-1} range,^{4, 28, 72, 73} and this definitely rules out the thiocarbamoyl azide structure. For the disubstituted derivatives of 5-amino-1,2,3,4-thiatriazole, therefore, only one structure is possible, i.e. structure 7. For the unsubstituted and monosubstituted compounds, however, it has been proposed²⁹ that they exist as the tautomeric 5-imino-1,2,3,4-thiatriazolines (8). For 5-methylamino-1,2,3,4-thiatriazole this possibility is ruled out by an investigation of its n.m.r. spectrum,⁷² and this result is probably generally valid for the 5-alkylamino-1,2,3,4-thiatriazoles. The unsubstituted compound has infrared absorption bands at 3135, 3257, and 1621 cm^{-1} , which may be assigned to two NH_2 stretching bands and a NH_2 deformation band, respectively; therefore it almost certainly exists as 5-amino-1,2,3,4-thiatriazole and not as 5-imino-1,2,3,4-thiatriazoline.

Lieber *et al.*⁷⁹ have come to the same conclusion by an investigation of the ultraviolet spectra and dipole moments of 5-amino-, 5-methylamino-, and 5-dimethylamino-1,2,3,4-thiatriazole. The dimethylamino derivative, in which no tautomerism is possible, shows the same characteristic absorption near 250 $\text{m}\mu$ as the unsubstituted compound and the monomethyl derivative. The dipole moments of the three compounds differ very little. These moments are quite large (5.8 Debye), showing that ionic resonance forms of type 9 contribute considerably to the structure of these compounds.

The most characteristic feature of the infrared spectra of all 5-mono- and -di-substituted-amino-1,2,3,4-thiatriazoles is a strong band in the 1540–1590 cm^{-1} range,^{31, 72, 73} which without doubt is due to the $\text{C}=\text{N}$ and $\text{N}=\text{N}$ stretching vibrations of the heteroaromatic ring system. Various infrared bands between 889 and 1122 cm^{-1} have been assigned to skeletal vibrations of the thiatriazole ring and a band at 1270–1300 cm^{-1} to the cyclic $=\text{N}-\text{N}=\text{N}-$ grouping²⁹ (cf., however, reference 73).



⁷⁹ E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.* **37**, 563 (1959).

Notes Added in Proof

Table I: Recently thiatriazoles with *o*-ethoxyphenyl, *o*-isopropoxyphenyl, *o*-butoxyphenyl, and *o*-isobutoxyphenyl groups as the 5-substituent have also been prepared; see reference 73.

Table III: Since this table was prepared R. G. Dubenko, I. N. Berzina, and P. S. Pel'kis [*Zh. Obshch. Khim.* **33**, 274 (1963)] have described eighteen 5-aryl-amino-1,2,3,4-thiatriazoles of which only five are listed in Table III. The melting points given for these five compounds differ considerably from those listed in Table III: *o*-tolyl, 117–118°; *p*-tolyl, 151–152°; *o*-methoxyphenyl, 109–110°; *p*-methoxyphenyl, 129–130°; and *p*-chlorophenyl, 162–163°.

Nucleophilic Heteroaromatic Substitution

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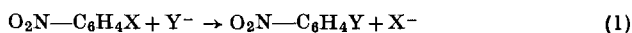
I. Introduction

In the field of nucleophilic aromatic substitution two classes of compounds are of special importance: nitrobenzene derivatives and *N*-heteroaromatic compounds. The reactions of both classes have long been known and the fundamental analogies between them have been recognized in many instances. Although heterocyclic chemistry has expanded tremendously through the years, the kinetic and mechanistic aspects of the subject were long neglected, in comparison with the corresponding aspects of benzenoid chemistry, in spite of the potential advantages offered by such studies of heterocyclics to theoretical

interpretations and also to synthetic methods. Practically all of the original papers on this subject have appeared within the last twenty years, over ninety percent of them within the last decade, which is indicative of the rapidly growing interest in the field. This growth, which has not been uniform, has been stimulated by theoretical interest and also by the special importance of some of the more highly reactive systems (e.g. *s*-triazine derivatives) in connection with dye chemistry and other applied topics. However fragmentary the results may be, one of the objects of this review is to present the status of nucleophilic substitution as based on the physical-organic studies which have been made with the principal types of heteroaromatic compounds.¹

Several *ad hoc* studies and discussions in recent years have been centered around the mechanism of aromatic substitution in nitro-activated benzene derivatives. The subject has been reviewed authoritatively.²⁻⁵

The reaction of a *p*- or *o*-nitrobenzene derivative with a nucleophilic reagent is generally first order with respect to each reactant and follows a bimolecular course according to Eq. (1). The reaction is then formally similar to the corresponding change at a saturated carbon ("*S_N2*"



mechanism) but differs substantially from it in that it involves attack of the reagent at an unsaturated aromatic carbon atom. Only in special cases (e.g. hydrolysis of diazonium ions), which will not be treated in this review, can the reaction follow a unimolecular mechanism resembling that frequently observed in substitutions at a saturated carbon atom ("*S_N1*" mechanism). The most widely accepted mechanism for nucleophilic aromatic substitution involves a change from *sp*² to *sp*³ hybridization of the attacked carbon atom (cf. 1).

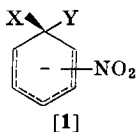
¹ A convenient classification of the main types of heteroaromatic compounds is that used by A. Albert in "Heterocyclic Chemistry." The Athlone Press, London, 1959.

² J. F. Bunnett and R. E. Zahler, *Chem. Rev.* **49**, 273 (1951).

³ P. B. D. de la Mare, *Progr. Stereochem.* **2**, 65 (1958).

⁴ J. Sauer and R. Huisgen, *Angew. Chem.* **72**, 294 (1960).

⁵ J. F. Bunnett, *Quart. Rev.* **12**, 1 (1958).



Recent evidence supports the view that at least in some cases structure 1 corresponds to an intermediate of finite stability and that the potential-energy *vs.* reaction-coordinate diagram in such cases consists of two maxima (transition states) separated by a minimum (intermediate).

The potential-energy diagram is a function, among other things, of the structure of the substrate. In particular, the stability, if any, of the intermediate depends on the degree of activation and the specific nature of the activating group. Owing to the essential analogies between the nitro- and the aza-activated aromatic systems, there is a dangerous tendency to consider the latter as *obvious* extensions of the former. One of the objects of this review is to discourage restrictive attitudes of this kind by trying to consider heteroaromatic nucleophilic substitution reactions in their own right and to look for both analogies and discriminating features in the behavior of the two classes of compounds. Some comments on the mechanism of these reactions are included in Section V following the description of the available body of experimental information. However, it can be anticipated that in many instances structure 1 can be assumed with confidence to approach either the configuration of a transition state or that of an intermediate of finite stability; this is often of great formal utility in the interpretation of experimental facts, even with the reservation that the exact physical nature of the transition state may be uncertain.

Aza-activation plays a major role in the studies which have been reported. The main properties associated with the aza group may be briefly summarized as follows. The polar effect of this group is qualitatively of the same type as that of the exocyclic nitro group in that both withdraw electrons from the ring by the inductive and the conjugative mechanisms. The steric requirements of a =N— system, however, in contrast to those of the relatively bulky nitro group, do not exceed those of an aromatic =CH— group. The major difference is in the basicity, which is a special case of a more general property, nucleophilicity. The nucleophilicity is of interest in that it opens the way to other types of activating groups (*N*-oxides, *N*-alkyl derivatives,

etc.), but the basicity is directly associated with the reactivity of *N*-heteroaromatic compounds since protons are readily available from many common reagents and/or solvents. Some authors⁶⁻⁸ who have been concerned with the nucleophilic substitution of halogeno-*N*-heteroaromatic compounds have also measured the corresponding ionization constants in water. These data, together with those for some of the fundamental ring systems,^{1, 9, 10} are assembled in Table I. They show that the halogeno substituents, which are the best-known of the groups that undergo displacement in substitution reactions, affect the basicity to a much greater extent when they are *alpha* than when they are *gamma* to the aza group. Thus 2-chloropyridine is less basic than pyridine by 4.5 p*K* units, while the decrease caused by chloro-substitution at the 4-position of quinoline is only 1.2 p*K* units. On the basis of the additivity of substituent effects,⁶ an estimated p*K_a* value of 0.4 for the weakly basic 2-chloroquinoline is obtained. Similarly, approximate values of the heretofore unknown basicities of the halogeno derivatives of all the other fundamental ring systems can be calculated. The basicities of 2-halogeno-5-nitropyridines were recently determined and found to be remarkably low, but they agree quite satisfactorily with the calculated values.⁸

Some investigations have been inspired by another special circumstance concerning the structure of the fundamental heteroaromatic rings: like the parent aromatic homocyclic hydrocarbons, these structures are readily amenable to theoretical treatment by the approximation methods of quantum mechanics. Quantitative studies are clearly desirable in this connection for a reliable test of the theory and, indeed, they have been utilized to this end.¹¹

Finally, a comment regarding nomenclature: reactions can obviously be named by specifying the individual reactants and products. However, if conciseness is required, use of Bunnett's method,¹²

⁶ E. Baciocchi and G. Illuminati, *Gazz. Chim. Ital.* **87**, 981 (1957).

⁷ E. Baciocchi, G. Illuminati, and G. Marino, *J. Am. Chem. Soc.* **80**, 2270 (1958).

⁸ J. D. Reinheimer, J. T. Gerig, R. Garst, and B. Schrier, *J. Am. Chem. Soc.* **84**, 2770 (1962).

⁹ H. C. Brown, D. H. McDaniel, and O. Häfliger, in "Determination of Organic Structures by Physical Methods" (E. A. Braude and F. C. Nachod, eds.), p. 567. Academic Press, New York, 1955.

¹⁰ A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," pp. 140 ff. Methuen, London, 1962.

¹¹ N. B. Chapman, *Chem. Soc. (London) Spec. Publ. No. 3*, 155 (1955).

¹² J. F. Bunnett, *Chem. Eng. News* **40**, 4019 (1954).

TABLE I

THE IONIZATION CONSTANTS OF SOME HETERO-
AROMATIC DERIVATIVES OF INTEREST IN
NUCLEOPHILIC SUBSTITUTION REACTIONS^a

Base	p <i>K</i> _a	Reference
Pyridine	5.17	9
Pyrimidine	1.30 ^b	10
Quinoline	4.81	6
Cinnoline	2.3 ^c	1
Quinazoline	3.5 ^c	1
Quinoxaline	0.72 ^b	10
Acridine	5.60 ^b	10
Halogenopyridines		
2-fluoro	-0.44	10
2-chloro	0.72	10
2-bromo	0.90	10
2-iodo	1.82	10
2-chloro-5-nitro	-2.97	8
2-iodo-5-nitro	-1.70	8
4-Chloroquinolines		
—	3.72	6
6-methoxy	3.93	6
7-methoxy	4.32	7
6-ethoxy	3.82	6
6-methyl	3.96	6
7-methyl	4.00	7
6-fluoro	2.95	6
7-fluoro	3.04	7
6-chloro	2.81	6
7-chloro	2.80	7
6-bromo	2.83	6
7-bromo	2.8	7

^a In water at 25°.

^b At 20°.

^c At 20–25°.

whereby the names of the incoming reagent and the displaced group are combined in a single word (e.g. methoxy-denitration, piperidino-defluorination), is recommended.

II. Course and Kinetic Form of the Reactions

A. THE LIMITS OF "NORMAL" SUBSTITUTION

As implied in the introduction, the term "nucleophilic aromatic substitution" as used by this author refers to "normal" substitutions, i.e., reactions consisting of essentially two stages, bond-making and bond-breaking *at the same carbon atom*, whatever their relative timing may be.¹³ There is another important, more complex type of substitution. This involves an elimination-addition mechanism and an aryne intermediate: characteristically, in this case, the nucleophilic reagent can become attached either to the carbon initially holding the displaced group or to a carbon *ortho* to it. The desirability of using a specific term to designate the latter type of reaction, such as "nucleophilic aromatic substitution *via* arynes,"¹⁴ is now apparent also for the aza-heteroaromatic substrates, in which the applicability of this reaction has recently been shown.^{15, 16}

The reactions of the halogeno derivatives of heteroaromatic systems with common nucleophilic reagents have in some cases been proved to be "normal" substitutions but in others were just assumed to be so, on admittedly reasonable grounds. It is of interest whether the present knowledge of the limits within which substitution *via* arynes operates reinforces the above assumptions.¹⁷ Caution is suggested by the fact that although the presence of activating moieties in the aromatic substrate favors "normal" substitution, halogenopyridines have, surprisingly, been found to undergo substitution *via* arynes. It is true that the latter mechanism is important only if the halogen occupies the less activated 3-position, but it also occurs to a minor extent in the reaction of 4-chloropyridine with lithium piperidide and piperidine.¹⁵ However, the fact that, as in 4-chloropyridine, "normal" substitution predominates greatly in the presence of a reagent that characteristically induces substitution *via* arynes indicates that all heteroaromatic compounds containing a leaving group at one of the most activated positions (i.e., *alpha* or *gamma* to the aza group) are unlikely to undergo other than "normal" substitution with such reagents as sodium alkoxides or amines (in the absence of alkali metal amide). This

¹³ This definition is comprehensive of both the common bimolecular and the infrequent unimolecular mechanism.

¹⁴ R. Huisgen and J. Sauer, *Angew. Chem.* **72**, 91 (1960).

¹⁵ T. Kauffmann and F. P. Boettcher, *Chem. Ber.* **95**, 1528 (1962).

¹⁶ R. J. Martens and H. J. den Hertog, *Tetrahedron Letters* 643 (1962).

¹⁷ J. F. Bunnett, *J. Chem. Educ.* **38**, 278 (1961).

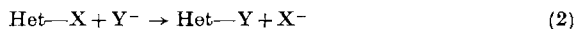
is in agreement with the cumulative preparative experience of heterocyclic chemistry.

For less activated substrates, specific tests are desirable. These are available in some cases. Thus Amstutz *et al.*¹⁸ showed that the reaction of 3-, 6-, and 8-bromoquinolines with piperidine at about 200° produced normal substitution products.

All the reactions discussed in this review are aromatic nucleophilic substitutions in the ordinary sense. These reactions are briefly described in the following sections with respect to their general kinetic features and mainly involve aza-activated six-membered ring systems, although a few studies of other heteroaromatic compounds are also available.

B. REACTIONS WITH ANIONS

In accordance with the observed behavior of nitro-activated aromatic compounds, in all cases tested the displacement of halogens from *N*-heteroaromatic carbon by such reagents as sodium methoxide¹⁹ and sodium ethoxide²⁰ in their respective alcohols [Eq. (2),



Het = heteroaryl residue] follow second-order kinetics, first order with respect to each reactant. Regular kinetics of this kind are also observed in the reaction of sodium arylsulfide in methanol provided that no free thiol is present (see Section II, D, 1, c). As to other heterocyclic systems, *N*-oxides²¹ and bromofuran derivatives²² show similar kinetic behavior.

In some cases the alkoxide ions have been used in large excess under pseudo-first-order conditions.^{23, 24}

Special interactions of the charged reagent with the substrate can lead to kinetic complications and to exceptional substrate reactivity. For example, the strongly basic alkoxide ion promotes ionization of

¹⁸ K. R. Brower, W. P. Samuels, J. W. Way, and E. D. Amstutz, *J. Org. Chem.* **18**, 1648 (1953).

¹⁹ G. Illuminati and G. Marino, *J. Am. Chem. Soc.* **80**, 1421 (1958).

²⁰ N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.* 1563 (1956).

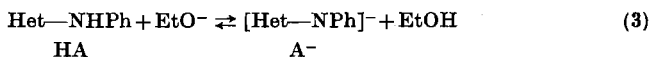
²¹ R. J. Boxer, Ph.D. Thesis Rutgers University, 1961; *Dissertation Abstr.* **22**, 66 (1961).

²² R. J. Petfield and E. D. Amstutz, *J. Org. Chem.* **19**, 1944 (1954).

²³ H. Ackermann and P. Dussy, *Helv. Chim. Acta.* **45**, 1683 (1962).

²⁴ K. R. Brower, *J. Am. Chem. Soc.* **80**, 2105 (1958); *ibid.* **81**, 3504 (1959).

the acidic hydrogen of an arylamino group, as is shown in Eq. (3) where NHPH is a substituent other than the leaving group.²³ Under the influence of this equilibrium, which produces the less reactive species A⁻, the reaction becomes slower than expected from the structure of



the conjugated acid HA and insensitive to increase in concentration of the charged reagent. The effect depends on the nature of both the aryl and the heterocyclic group as they control the acidity of the amino hydrogen. Similar behavior is observed if OH⁻ in water instead of EtO⁻ in 80% ethanol is used as the nucleophile. Here a more complete treatment takes into account the ionization constant of HA in the kinetic expression for the observed reaction rate.

An interesting kinetic study was carried out under pseudo-first-order conditions for the base hydrolysis of the three isomeric *N*-methyl-cyanopyridinium salts, a reaction that leads partly to CN⁻ replacement and partly to the formation of a carboxamido derivative.²⁵

Detailed kinetic studies of the substitution reactions of anions with heterocyclic compounds to include, for example, the effects of solvent, added salts, and ion pair formation have not been made as yet.

C. REACTIONS WITH UNCHARGED SPECIES

Reactions with uncharged species such as amines, alcohols, and water offer frequent opportunities for investigations under pseudo-first-order conditions since many of these reagents are suitable solvents. However, the reactions with amines have often been investigated in alcohols²⁶ and in non-hydroxylic solvents^{18, 27–29a} and have been found to follow second-order kinetics.

When a proton is released during the reaction and transferred to a base B, as shown in Eq. (4), the presence of a basic substrate may cause

²⁵ J. W. Patton, Ph.D. Thesis, University of Wisconsin, 1961; *Dissertation Abstr.* **22**, 745 (1961).

²⁶ R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.* **437** (1952).

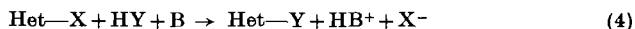
²⁷ K. Matsui, K. Hagiwara, and Y. Soeda, *Yuki Gosei Kagaku Kyokai Shi* **18**, 184 (1960).

²⁸ M. Goi, *Yuki Gosei Kagaku Kyokai Shi* **18**, 327 (1960).

^{29a} G. Illuminati and G. Marino, *Chem. Ind. (London)* 1287 (1963).

^{29b} G. Illuminati and G. Marino, *Tetrahedron Letters* 1055 (1963).

autocatalytic phenomena; these will be discussed separately (see Section II, D). For some reactions of thiols and amines in hydrocarbons, third-order kinetics were suspected³⁰ or definitely established.³¹



Second-order kinetics are reported for the reactions of halogenoquinoline *N*-oxides with piperidine in several solvents³² and of halogeno-nitrothiophenes with piperidine in ethanol.³³

Ammonolysis of 2-chlorobenzothiazole in liquid ammonia was studied by Lemons *et al.*³⁴ and found to be approximately first-order with respect to this substrate at the fairly high concentrations used. The actual nucleophilic reagent was, as expected, the neutral species NH_3 , and reaction *via* the amide ion NH_2^- arising from the autoprotolysis equilibrium [Eq. (5)] was excluded on the grounds that addition of ammonium chloride did not depress the reaction rate. In accordance with this interpretation and in connection with the existence of aromatic substitutions other than "normal" it is of interest that 2-chlorobenzothiazole was found to react differently with sodamide, although the products were unidentified in this case.



Salt effects in the above reaction were investigated extensively. They are negligible on the reaction rate but appreciable on the activation energy which increased by 1.3 to 2.2 kcal/mole for salt concentrations rising to 0.31*M*.

In connection with the biological activity of *s*-triazines, Burchfield and Storrs³⁵ investigated the reaction of 2,4-dichloro-6-(*o*-chloroanilino)-*s*-triazine with over sixty amino acids, peptides, and related

³⁰ G. Grassini and G. Illuminati, *Gazz. Chim. Ital.* **86**, 437 (1956).

³¹ B. Bitter and H. Zollinger, *Angew. Chem.* **70**, 246 (1958); *Helv. Chim. Acta* **44**, 812 (1961).

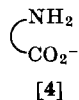
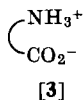
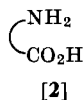
³² T. Okamoto, H. Hayatsu, and Y. Baba, *Chem. Pharm. Bull. (Tokyo)* **8**, 892 (1960).

³³ D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim. (Rome)* **52**, 1156 (1962).

³⁴ J. F. Lemons, R. C. Anderson, and G. W. Watt, *J. Am. Chem. Soc.* **63**, 1953 (1941); J. F. Lemons, P. M. Williamson, R. C. Anderson, and G. W. Watt, *ibid.* **64**, 467 (1942).

³⁵ H. P. Burchfield and E. E. Storrs, *Contrib. Boyce Thompson Inst.* **18**, 395 (1956); *ibid.* **19**, 169 (1957).

high-molecular weight compounds. These are a special class of amino-nucleophiles which can exist in the form of several species (cf. 2-4) in aqueous solution. Species 3 is in equilibrium with the others and is



unreactive. Under the experimental conditions used, species 4 predominated over 2. Significant discrepancies were noticed on attempting to correlate the structure of the amino acid with the second-order rate constants calculated from the overall reagent concentration. Since the active nucleophile was 4, a modified expression for the rate constant allowing for the above mentioned equilibrium was necessary [Eq. (6)], where k , K , and a_H^+ are the rate constant for the reaction

$$k_{app} = \frac{kK}{K + a_H^+} \quad (6)$$

with the predominating species, the apparent dissociation constant of the group acting as a nucleophile, and the hydrogen ion activity of the medium, respectively. This shows that an over-all second-order rate constant (k_{app}) can conceal a reaction of greater complexity. A further complication of interest was that sulfhydryl-containing amino acids (cysteine and glutathione) were found to be the most reactive amino acids, probably as a result of an effective competition of the SH (or S⁻) group in nucleophilic attack.

A few studies on solvolyses by alcohols³⁶ and by water are available. The hydrolyses studied include displacement of alkylamino groups from acridine antimalarials^{37, 38} and of halogen from other systems.³⁹ In all cases, these reactions appeared to be first-order in the heterocyclic substrate. By a detailed examination of the acid hydrolysis of 2-halogeno-5-nitropyridine, Reinheimer *et al.*⁸ have shown that the reaction rate varies as the fourth power of the activity of water, providing direct evidence that the only reactive nucleophile is neutral water, as expected.

From the overall kinetic evidence, a bimolecular mechanism is

³⁶ K. Matsui, K. Hagiwara, and A. Hayashi, *Yuki Gosei Kagaku Kyokai Shi* **18**, 97 (1960); K. Matsui and J. Seino, *ibid.* **18**, 105 (1960).

³⁷ K. Noda, *J. Pharm. Soc. Japan* **64**, 6 (1944); *Chem. Abstr.* **45**, 5693 (1951).

³⁸ D. L. Hammick, S. F. Mason, and G. W. Meacock, *J. Chem. Soc.* 4745 (1952).

³⁹ H. Koopman, *Rec. Trav. Chim.* **81**, 465 (1962).

generally accepted for reactions of the type considered in this Section, even in those cases studied under pseudo-first-order conditions. There is other evidence for this conclusion, such as the influence of substituents on reaction rates. This justifies conversion of pseudo-first-order into second-order rate constants, a practice particularly useful in structural comparison.⁴⁰

D. CATALYTIC AND AUTOCATALYTIC PHENOMENA

1. Acid Catalysis

a. *General Remarks.* A distinctive structural feature of most heteroaromatic substrates, *viz.* the basicity of the aza group, is responsible for the occurrence of acid catalysis in nucleophilic substitution. The phenomenon essentially involves the conversion of the aza group into the strongly electron-attracting $=\text{NH}^+$ moiety. This has a pronounced effect on reaction rates, which is quantitatively similar to that found for a quaternized nitrogen group as a part of the heterocyclic ring ($=\text{NR}^+$) or as an exocyclic substituent ($-\text{NR}_3^+$).

Interplay between a number of factors may lead to anything from a large enhancement of rate to a complete inhibition of acid catalysis. Most important, both substrate and nucleophile compete for the proton, so that relative base strengths and concentrations play a major role in the kinetic course. Further, the solvent also plays an important role by either acting as a base itself or by affecting relative base strengths and solubilities of the reactants and products. Finally, the stoichiometry of the reaction may be such as to produce strong acids among the products: here the effect occurs even in the absence of initial acid and the reaction is autocatalytic.

Autocatalysis may arise when the nucleophilic atom of the reagent is bound to a hydrogen atom which is eventually eliminated during the reaction. This occurs with neutral reagents such as primary or secondary amines, thiols, and alcohols. If the displaced group (usually an anion) is a sufficiently weak base, the proton is effectively transferred to any basic reactant. Hence, the best known examples of autocatalysis involve chloro-*N*-heteroaromatic compounds as the substrates.

b. *Reactions with Amines.* Both acid catalysis and autocatalysis were first recognized by Banks⁴¹ through an extensive, semi-

⁴⁰ J. F. Bunnett, in "Technique of Organic Chemistry" (A. Weissberger, ed.), Vol. VIII, Chapter 6. Interscience, New York, 1961.

⁴¹ C. K. Banks, *J. Am. Chem. Soc.* **66**, 1127 (1944).

quantitative study of the reaction of several halogeno derivatives of pyridine, thiazole, pyrimidine, and *s*-triazine with anilines in aqueous solution. For example, the reaction rate of 2-chloro-4,6-diamino-*s*-triazine with aniline was found to be increased markedly by the addition of 0.01 equivalent of strong acid and to decrease to zero on addition of one equivalent of strong base. The effect was just as marked whether the starting material was suspended in water or dissolved in 10% aqueous acetone.

These observations were confirmed by Chapman *et al.*^{26, 42} and extended to other reagents such as piperidine and morpholine. The ability of the proton to become selectively distributed between reagent and substrate is shown in the following examples. In ethanol solution and with a two- to four-fold excess of the amine, the reactions of the chloropyrimidines and their methyl derivatives with aniline are autocatalytic in contrast to those with the more basic reagents morpholine and piperidine. 4-Chloroquinoline is a stronger base than 2-chloroquinoline (see Section I) and is subject to autocatalysis with piperidine or morpholine; however, the basicity difference of the two nucleophiles is sufficient to allow 2-chloroquinoline to show autocatalysis behavior only with the weaker base, morpholine.

The behavior of the chloropyridines and their nitro-substituted derivatives is apparently similar, the 2-chloro compounds having less tendency to show autocatalytic behavior than the 4-chloro analogues with a given nucleophile. For 4-chloropyridines the reaction may be further complicated by self-quaternization.^{20, 28, 43}

In many instances the degree of solubility of the acidic reaction products determines whether autocatalysis occurs. Thus, the reaction of 5-chloroacridine with piperidine is autocatalytic in ethanol but not in toluene where most of the piperidine hydrochloride formed precipitates.¹⁸

c. *Reactions with Thiols.* In reactions with amines autocatalysis may or may not occur depending on the basicity of the amine, but it seems to be more general when non-basic nucleophilic reagents such as thiols can react in their initially unionized form.^{30, 44} This is the case for the reaction of a number of 2- and 4-chloroquinolines with *p*-thiocresol in toluene solution. The quinolinium chloride produced

⁴² N. B. Chapman and C. W. Rees, *J. Chem. Soc.* 1190 (1954).

⁴³ K. R. Brower, J. W. Way, W. P. Samuels, and E. D. Amstutz, *J. Org. Chem.* **19**, 1830 (1954).

⁴⁴ G. Illuminati and L. Santucci, *Gazz. Chim. Ital.* **83**, 1106 (1953).

has only a limited solubility and eventually separates as a crystalline solid. Detailed study revealed that the extent of autocatalysis, apparent in all the compounds tested, depends on the basicity of the starting quinoline and on the steady-state concentration of the acidic reaction product formed. A low basicity of the substrate (2-chloro-quinoline) combined with a low solubility of the product results in only a slight autocatalytic effect and second-order kinetics are reached after a few percent reaction. However, a higher basicity of the substrate (4-chloro-7-*p*-tolylthioquinoline) combined with a higher solubility of the acidic product causes a kinetic complexity throughout the process and marked reactivity inversions with respect to the order expected from theory.⁴⁵ Very powerful autocatalytic effects ensue in hydroxylic solvents.^{29b}

d. *Solvolytic Reactions.* These reactions can be acid-catalyzed unless the solvent is sufficiently basic to compete effectively with the substrate for the proton. Thus, with respect to a given substrate, susceptibility to acid catalysis should decrease in the order: alcohols > water > piperidine. Accordingly, piperidinolysis is seldom accompanied by autocatalysis.

In the hydrolysis of acridine antimalarials, the role of the protonated species of the substrate appeared to be important even in aqueous solution buffered at pH 7.3, i.e., under conditions of physiological interest.³⁸ Moreover, out of the three possible modes of reaction mathematically possible ($\text{H}_3\text{O}^+ + \text{B}$, $\text{H}_2\text{O} + \text{BH}^+$, and $\text{OH}^- + \text{BH}_2^{+2}$, where B is the basic substrate) the one not involving the protonated substrate can be ruled out on structural grounds.

Spectroscopic evidence⁴⁶ indicates that protonation of 2-fluoro- and 2-chloro-quinoline is not appreciable in 0.01*M* aqueous hydrochloric acid. Protonation becomes evident in more strongly acidic solution in the case of the chloro compound without any accompanying decomposition, but the fluoro compound hydrolyzes to carbostyryl under the latter conditions. The hydrolysis is acid-catalyzed, but it is doubtful whether protonation on the heterocyclic nitrogen is responsible, owing to its low basicity (presumably below that for the chloro compound). An alternative explanation in this case would be hydrogen bond formation with fluorine, $\text{Ar}-\text{F} \cdots \text{H}-\text{O}^+\text{H}_2$.

Ethanol is a rather poor nucleophilic reagent but, when used as a

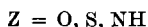
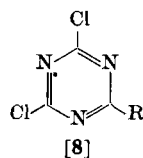
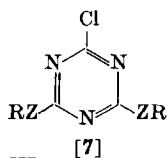
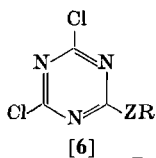
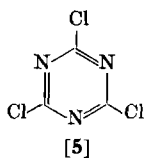
⁴⁵ G. Illuminati and G. Marino, *Atti Acad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **21**, 318 (1956).

⁴⁶ W. K. Miller, S. B. Knight, and A. Roe, *J. Am. Chem. Soc.* **72**, 4765 (1950).

solvent, may attack particularly reactive substrates such as a 4-chloro-3-nitropyridine²⁶ and a number of derivatives of 2-chloro-5-nitropyridine.⁴⁷ In favorable cases, subsequent protonation of the substrate (4-chloro-3-nitropyridine) occurs sufficiently to cause autocatalysis. Chapman and Rees⁴² assume the intervention of ethanolysis and thus explain the occurrence of autocatalysis in some less obvious cases, such as the reaction of chloropyrimidines and 4-chloroquinazoline with pyridine, a nucleophile not involving proton release.

2. The Behavior of *s*-Triazine Derivatives

a. *Acid Catalysis.* In this and the following paragraph, it is shown that the reactions of cyanuric chloride and its derivatives offer a good illustration of the roles of the substrate, nucleophile, reaction product, and solvent in catalytic phenomena and the subtle interplay of these factors whether or not sensitiveness to catalysis results. These reactions have recently been studied by Matsui *et al.*^{27, 36, 48} and Goi.^{28, 49, 50} As noted previously, an α -chlorine atom renders a ring-nitrogen atom very weakly basic. Cyanuric chloride (5) is a very weak base both because *s*-triazines are of low basicity and because each of the ring-nitrogen atoms is *alpha* to two chlorine atoms. Hence, this compound should be insensitive to acid catalysis or acid autocatalysis and this has been observed for the displacement of the first chlorine atom with alcohols in alcohol-acetone solution³⁶ and with water⁴⁸ (see, however, Section II, D, 2, *b*).



Compounds of type 6 containing ZR substituents with a *p*-electron pair on the Z atom bound to the ring carbon ($Z = O, S, NH$) are formed by displacement of the first chlorine atom of cyanuric chloride by well-known nucleophiles. Their basicity should be greater than that of cyanuric chloride because of the mesomeric electron release of the ZR

⁴⁷ N. B. Chapman, D. K. Chandhury, and J. Shorter, *J. Chem. Soc.* 1975 (1962).

⁴⁸ K. Matsui and I. Sachamoto, *Yuki Gosei Kagaku Kyokai Shi* **18**, 175 (1960).

⁴⁹ M. Goi, *Yuki Gosei Kagaku Kyokai Shi* **18**, 332 (1960).

⁵⁰ M. Goi, *Yuki Gosei Kagaku Kyokai Shi* **18**, 337 (1960).

substituent to the *alpha* and *gamma* ring-nitrogen atoms but still low because of the effect of the two remaining chlorine atoms. The reactions of these compounds (**6**) with nucleophilic reagents are of special interest in connection with acid catalysis. Their solvolysis in ethanol-acetone solution shows both acid catalysis and autocatalysis³⁶ whereas hydrolysis in aqueous acetone (not examined in the presence of acids) does not seem to be autocatalyzed.³⁹ Compounds with phenyl substituents (**8**; R = C₆H₄X), similar to **6**, show reactivity well correlated with X and no complications from autocatalysis. If no acid catalysis occurs in the hydrolysis of these compounds, this might be explained by the markedly greater basicity of water compared with alcohols⁵¹ which inhibits protonation of weakly basic heterocyclic substrates.

The reactivities of compounds of type **6** with aniline in acetone correlate quite well with substituent effects, and autocatalysis is unimportant here.²⁷ In the less polar tetrahydrofuran, where the hydrochloride is only partly soluble, the reaction shows autocatalysis when aniline and *p*-chloro aniline are reactants but not when the more basic *p*-toluidine is involved. In these cases the solubility of the acidic product may also influence the differential behavior observed.

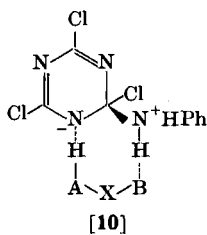
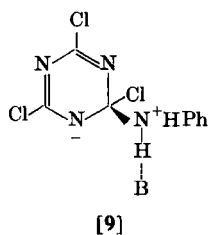
Finally, with compounds of type **7**, which have one chlorine atom and two ZR substituents, the reactions are, as expected, more frequently acid catalyzed than with compounds of type **6**: e.g., the reaction with aniline in acetone is distinctly acid catalyzed.²⁷ Again, reactions still occur, e.g., with benzylamine in tetrahydrofuran, in which autocatalysis is absent,^{28, 49} possibly because of a combination of the marked basicity of the reagent and the low solubility of the acidic product.

b. *Base Catalysis and Bifunctional Catalysis.* Acid catalysis in the above reactions of *s*-triazine derivatives consists essentially of an activation of the substrate through the equilibration of the proton among the basic species present in solution *after* the proton was produced in (or added to) the system. Since the production of the proton involves the rupture of a covalent bond (RZ—H) in the nucleophilic reagent, the latter process should be, under suitable conditions, kinetically important in the displacement at the aromatic center. Such results were obtained recently by Bitter and Zollinger^{31, 52} who investigated the reaction of 2,4,6-trichloro-*s*-triazine with aniline in benzene solution.

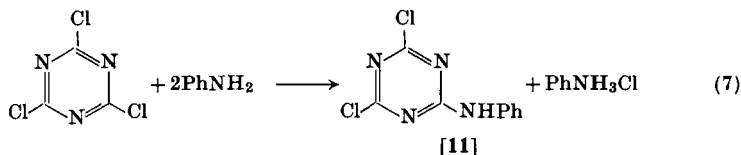
⁵¹ C. E. Newall and A. M. Eastham, *Can. J. Chem.* **39**, 1752 (1961).

⁵² H. Zollinger, *Angew. Chem.* **73**, 125 (1961).

In this solvent the reaction is catalyzed by small amounts of trimethylamine and especially pyridine (cf. **9**). The same effect occurs in the reaction of *N*-methylaniline with 2-*N*-methylanilino-4,6-dichloro-*s*-triazine. In benzene solution, the amine hydrochloride is so insoluble that the reaction could be followed by recovery of the salt. However, this precluded study under Bitter and Zollinger's conditions of catalysis by strong mineral acids in the sense of Banks (acid-base pre-equilibrium in solution). Instead, a new catalytic effect was revealed when the influence of organic acids was tested. This was assumed to depend on the bifunctional character of these catalysts, which act as both a proton donor and an acceptor in the transition state. In striking agreement with this conclusion, α -pyridone is very reactive and *o*-nitrophenol is not. Furthermore, since neither γ -pyridone nor *p*-nitrophenol are active, the structure of the catalyst must meet the conformational requirements for a cyclic transition state. Probably a concerted process involving structure **10** in the rate-determining step



is a convenient path where HAXB can act as a bifunctional catalyst but is not necessarily a strong acid or a strong base. This view explains the slight autocatalytic course of the reaction with aniline (but not *N*-methylaniline) [Eq. (7)], for which product **11** would act as a bifunctional catalyst, the NHPh group being the acidic moiety and the ring-nitrogen atom the basic center.



Structures **9** and **10** might correspond to transition states for the decomposition of the labile chemical intermediates supposedly involved in the reaction (see also Section V). The use of benzene seems

to be an essential condition for revealing the effects illustrated above since little assistance can be expected from a non-polar, poorly solvating solvent for the several individual stages involved, i.e., abstraction of hydrogen from the reagent, removal of the leaving group, and the change of activation of the aza group.

3. Role in Synthetic Work

An understanding of acid catalysis or autocatalysis in the reaction of basic *N*-heteroaromatic compounds with non-charged nucleophilic reagents sometimes leads to substantial changes in preparative procedures. Thus, although strong acids are liberated in the reaction and the nucleophilicity of the reagents can be inhibited by protons, the well-established practice of adding bases can often be profitably changed by adding traces of strong acids⁴¹ or just mixing the reagents without any solvent.⁵³ Consideration of catalytic phenomena has been found useful in several other instances.^{50, 52}

III. Reagent and Solvent Effects

Efforts to establish a theoretical explanation of the reactivity of nucleophilic reagents have centered on correlations with intrinsic electron-donor properties which are the fundamental basis of nucleophilicity.^{54, 55} According to Edwards and Pearson,^{55c} in general, such properties include basicity, polarizability, and the presence of unshared electron pairs on the atom adjacent to the nucleophilic atom of the reagent. When only the first two of these properties are operative, Eq. (8), which was proposed by Edwards,^{55b} has proved successful in

$$\log (k/k_0) = \alpha P + \beta H \quad (8)$$

establishing linear free-energy relationships (k/k_0 is the rate relative to water, P is the polarizability, H is the basicity, and α and β are constants). The existence of short-range London forces, which can be demonstrated under suitable conditions, has been recently shown to play a definite role in nucleophilicity.⁵⁶

The reactivity of a nucleophilic reagent may also depend on stereochemical conformation, degree of solvation and hydrogen-bonding,

⁵³ G. Grassini and G. Illuminati, *Ric. Sci.* **25**, 296 (1955).

⁵⁴ C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.* **75**, 141 (1953).

⁵⁵ (a) J. O. Edwards, *J. Am. Chem. Soc.* **76**, 1540 (1954); (b) *ibid.* **78**, 1819 (1956); (c) J. O. Edwards and R. G. Pearson, *ibid.* **84**, 16 (1962).

⁵⁶ J. F. Bunnett, *J. Am. Chem. Soc.* **79**, 5969 (1957).

and on other specific interactions with the substrate. Hence several other factors may actually be involved in reagent reactivity in addition to the basicity which has long been recognized as a major factor. This conclusion also follows from studies of heteroaromatic substitution reactions.

A. THE NUCLEOPHILICITY OF AMINES

As a first approximation, within a given family of nucleophilic reagents, such as amines, basicity changes are mainly responsible for differences in nucleophilic power. The pK_a values of some of the more familiar amines¹⁰ together with the rate constants for some of their reactions with chloroheteroaromatic compounds^{26, 42, 49, 50} are shown in Table II. We can see that a correlation exists between the two properties but it is only qualitative in character; the basicity order (in water) is piperidine \gg benzylamine $>$ morpholine \gg pyridine $>$ aniline, and the nucleophilic reactivity order (in tetrahydrofuran) is benzylamine $>$ aniline and (in ethyl alcohol) is piperidine $>$ morpholine \gg aniline $>$ pyridine.

The data show that in some cases basicity has a strong influence on reactivity. For example, the reaction of 2-chloropyridine derivatives with piperidine is about 3000 times as fast as that with pyridine; the basicity change involved is in the order of 6 pK_a units. However, piperidine is only 4 times as reactive as morpholine with 2- or 4-chloropyrimidine as the substrate, although ΔpK_a in these cases is still fairly large, 2.5 units. Furthermore, even the qualitative correlation sometimes fails, and aniline is more reactive than pyridine in contrast to the expectations from their basicities.

The position of aniline in the above reactivity order deserves special comment. Aniline is less basic than pyridine by a relatively small factor, 0.65 pK_a units, but is appreciably more polarizable^{56a}; it then seems likely that the inverted order of reactivity is caused by the polarizability term in accordance with Edwards' equation. If this is correct, in the reactivity order piperidine $>$ aniline $>$ pyridine, inversion with respect to basicity appears to result from an *abnormally high* reactivity of aniline rather than from a particularly low reactivity of pyridine. This view differs from that based on relative steric requirements of the reagents,²⁶ but other factors besides basicity and polarizability may well contribute to the quantitative experimental picture.

From the data reported in Table II it can be seen that a specific structural effect of the substrate plays a role in determining the appa-

TABLE II

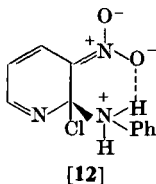
SPECIFIC RATE CONSTANTS^a FOR THE REACTION OF CHLOROAZINES WITH VARIOUS AMINES

In water, at 25 ^{ob}		10 ⁴ <i>k</i> in ethyl alcohol, at 55 ^{oc}			10 ² <i>k</i> in tetrahydrofuran, at 40 ^{od}
Reagent	p <i>K</i> _a	2-Chloro- pyrimidine ^e	2-Chloro- 3-nitro- pyridine	2-Chloro- 5-nitro- pyridine	2,4-Dichloro- phenylamino- <i>s</i> -triazine
Piperidine	11.22	6.70	184.1	281.8	—
Benzylamine	9.34	—	—	—	93.1
Morpholine	8.70	1.52	—	—	—
Pyridine	5.23 ^f	—	0.0103	0.0197	—
Aniline	4.58	—	0.169	0.119	2.40

^a *k* values expressed in liter × mole⁻¹ × sec⁻¹.^b From ref. 10.^c From refs. 26 and 42.^d From refs. 49 and 59.^e At 30°.^f At 20°.

rent reactivity of the reagent. With pyridine and piperidine as the reagents, the rate ratios for *ortho*-nitro- to *para*-nitro-substituted 2-chloropyridine ($k_{3-\text{NO}_2}/k_{5-\text{NO}_2}$) are less than unity and similar in value (0.5 and 0.6, respectively), but this ratio is nearly three times as great in the case of aniline (1.4). Again, aniline seems to possess a rate-enhancing factor which, when considered with respect to the $k_{3-\text{NO}_2}/k_{5-\text{NO}_2}$ ratio, appears to be associated with the presence of an *ortho*-nitro group. From this and from the activation parameters (see Section VII), pyridine and piperidine appear to show similar behavior; the Arrhenius frequency factor is practically constant ($\log A = 6.1\text{--}6.3$) and the variation in reactivity depends exclusively on the energies of activation. By contrast, the frequency factors for the two aniline reactions differ from each other and from the values for the other two nucleophiles ($\log A = 3.8\text{--}5.0$).

Several explanations are possible for the relatively high $k_{3-\text{NO}_2}/k_{5-\text{NO}_2}$ ratio for the reaction with aniline. Because of the relatively high polarizability of the reagent, a rate-enhancing interaction with the adjacent, polarizable nitro group involving London forces⁵⁶ could account for this moderate effect. Another possible factor is hydrogen bonding in the transition state between the N—H bond of the nucleophile and an oxygen atom of the nitro group (structure **12**) or the aza-nitrogen atom. In this case, the trend of the $k_{3-\text{NO}_2}/k_{5-\text{NO}_2}$ ratios suggests that an *ortho*-nitro group has a greater



tendency toward hydrogen bond formation than does an α -aza group (which is consistent with stereochemical requirements) and that the attack of aniline would be more efficiently assisted by hydrogen bonding than that of piperidine.

The idea that hydrogen bonding, as a special *ortho* effect of the substrate, may be involved in the transition state of the reactions with amines was first proposed by Chapman *et al.*²⁶ Attempting to test this hypothesis, Hawthorne⁵⁷ investigated the hydrogen-isotope effect in the reaction of *o*- and *p*-chloronitrobenzene with

⁵⁷ M. F. Hawthorne, *J. Am. Chem. Soc.* **76**, 6358 (1954).

N-deuteriopiperidine in xylene but found no effect. de la Mare³ questioned whether isotope effects should be expected here at all. It seems to this author that any effect of weakening the N—H bond on the rate of nucleophile attack on the substrate should depend on the extent of N—H bond-breaking in the rate-determining step of the reaction. If the hydrogen bond in the transition state involves only a small amount of N—H bond-breaking, it may well be perceptible in the measured rate but not in the isotope effect. However, starting from a "normal" hydrogen-bond interaction, sometimes further N—H bond-breaking may occur in the rate-determining step. One such case is the reaction of cyanuric chloride with aniline in benzene solution where Zollinger *et al.*^{31, 52} provided evidence for base and bifunctional catalysis and for small, but probably significant, isotope effects.

As pointed out by Chapman *et al.*,²⁶ the steric requirements of the reagents and the degree of solvation of the substrate at the reacting center should also be considered when comparing the nucleophilicities of different amines toward different substrates. The large number of factors which may be involved clearly call for much more work in this area.

In spite of the potential complexity of the general problem, even when restricted to the reagent family of amines, the nucleophilicities of such series as *meta*- and *para*-substituted pyridines and anilines appear to correlate very closely with the expected substituent effects and with the basicities. This has been verified in the following cases:

(1) The reaction of pyridines ($R = H$, *m*- and *p*-CH₃) with 2-chloro-3-nitro-, 2-chloro-5-nitro-, and 4-chloro-3-nitro-pyridines.⁵⁸

(2) The reaction of anilines ($R = H$, *m*- and *p*-CH₃, *m*- and *p*-halogeno, *m*-NO₂, *p*-OCH₃, *p*-OC₂H₅) with 2-chloro-3-nitro-, 2-chloro-5-nitro-, 2-chloro-3-cyano-5-nitro-, 2-chloro-3-cyano-6-methyl-5-nitro-, and 2-chloro-3-cyano-4,6-dimethyl-5-nitro-pyridines.^{26, 47}

(3) The reaction of anilines ($R = H$, *m*- and *p*-CH₃, *p*-OCH₃, *p*-Cl) with 2-chloro-4,6-diphenoxy-*s*-triazine.⁵⁹

In all cases where a sufficiently large number of substituents has been tested, a linear free-energy correlation is found with Hammett's σ -constants.⁶⁰ The reaction constants are fairly high, the values rang-

⁵⁸ E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.* 3392 (1953).

⁵⁹ K. Matsui, K. Hagiwara, A. Hayashi, and Y. Soeda, *Yuki Gosei Kagaku Kyokai Shi* 18, 53 (1960).

⁶⁰ L. P. Hammett, "Physical Organic Chemistry." McGraw-Hill, New York, 1940; H. H. Jaffé, *Chem. Rev.* 53, 191 (1953).

ing from -3.4 for reaction No. 2 in methanol at 10° to -2.5 for reaction No. 3 in acetone at 35° .

The good correlation found between the reactivities of 2-chloro-3-cyano-5-nitropyridine and the polar effects of the substituents on the aniline reagent has enabled Chapman and his co-workers⁴⁷ to illustrate the steric requirements of the reagent by including in their studies

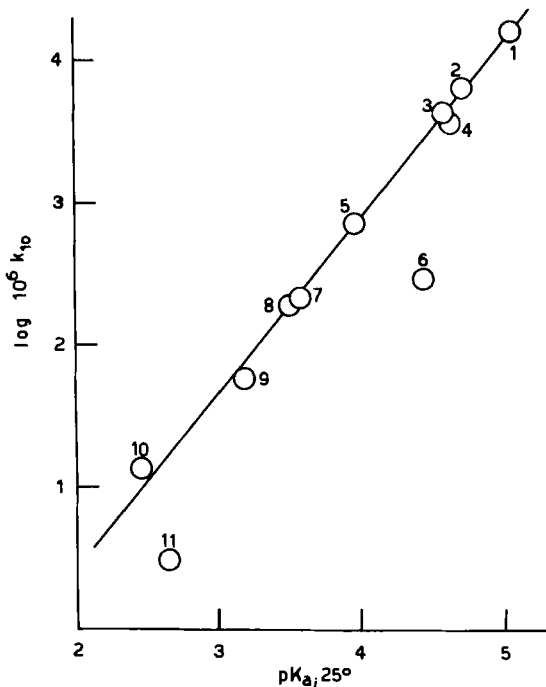


FIG. 1. Correlation of reactivity data ($\log k$) for the reaction of 2-chloro-3-cyano-5-nitropyridine with substituted anilines and the ionization data ($\log K_a$) for the latter compounds. (1, *p*-Me; 2, *m*-Me; 3, H; 4, *p*-F; 5, *p*-Cl; 6, *o*-Me; 7, *m*-F; 8, *m*-Cl; 9, *o*-F; 10, *m*-NO₂; and 11, *o*-Cl.) [From Chapman *et al.*,⁴⁷ by permission of The Chemical Society.]

some *ortho*-substituted anilines. The steric requirements of the attacking reagent on the aromatic substrate in alcohol would be expected to be greater than in the case where the substrate is the hydrogen ion in water. This is indeed found on correlating the nucleophilic reactivities with the basicities (Fig. 1). The plot of the $\log k$'s vs. pK_a 's for the reaction of 2-chloro-3-cyano-5-nitropyridine with substituted anilines is linear for all the *m*- and *p*-substituents tested. For *ortho*-substituents,

fluorine falls almost on the line whereas chlorine and methyl deviate markedly and fall below the line. The rate-depressing effect in the case of the methyl group is immediately apparent since it overcomes the opposing polar effect, so that *o*-toluidine reacts slower than aniline. The deviations are in the order expected from the group sizes, i.e., $\text{CH}_3 > \text{Cl} > \text{F}$. Chapman points out that the reactivities for these groups are accompanied by a change in $\log A$ (increase) in the case of the methyl group but there is no change in the two other groups with respect to all the other terms in the series. A compensation of opposing factors, a steric effect and steric inhibition of solvation, has been suggested in the case of chlorine to explain the apparent inconsistency with the free-energy of activation.

B. DEPENDENCE OF SOLVENT EFFECTS ON THE STRUCTURE OF THE SUBSTRATE

Some aspects of solvent effects in heteroaromatic substitutions in connection with catalytic phenomena are treated in Section II, D. Although solvents of widely different types have been employed in studies of the kinetics of these reactions, there has been relatively little effort to investigate their effects on the rates in a systematic manner. Nevertheless, there are indications that a better understanding of these effects would have important bearings on the elucidation of reaction mechanisms and on the development of synthetic procedures. den Hertog *et al.*⁶¹ found, for example, that in the reaction of 2,4,6-tribromopyridine with sodium phenoxide replacement of an α -bromo group predominates in phenol solution whereas both α - and γ -bromo groups are displaced in water. Butanol favors displacement by ammonia of an α -bromo group from the same compound, whereas water causes displacement of both α - and γ -bromo groups in approximately equal amounts.

Several general factors should be considered when dealing with solvent effects on reaction rates. The degree of solvation of the nucleophilic reagent and of the leaving group are particularly important. Parker⁶² has shown that for anionic reagents the order of nucleophilicity changes drastically depending on whether the solvent is able to hydrogen bond with the reagent (hydroxylic solvents) or not (dipolar aprotic solvents). The fluoride ion acts as a strong nucleophile

⁶¹ H. J. den Hertog and A. P. de Jonge, *Rec. Trav. Chim.* **67**, 385 (1948); H. J. den Hertog and C. Jouwersma, *ibid.* **72**, 44 (1953).

⁶² A. J. Parker, *Quart. Rev. (London)* **16**, 163 (1962).

under the latter conditions and can displace the chloride ion from several substrates including heteroaromatic compounds such as chloropyridines⁶³ and 2,4,6-trichloropyrimidine.⁶⁴ Conversely, fluoride ion removal from the substrate is greatly assisted by hydroxylic solvents but may be more difficult in dipolar aprotic solvents.⁶⁵

Although hydrogen bond solvation involving a lone-pair of electrons on the nucleophilic atom (amines) would be expected to lower the nucleophilicity of the reagent, with other non-charged nucleophiles such as thiophenol hydrogen bonding involving the acidic hydrogen may cause rate-enhancement. Thiophenol is a poor proton donor but its ability to form hydrogen bonds with the solvent or other basic species has been recognized in some instances⁶⁶ and may also be related to some observed autocatalytic effects (Section II, D, 1, c).

Solvent effects also depend on the ground-state structure of the substrate and on the transition-state structure, as is shown below. Here let us merely note that *N*-heterocyclic compounds tend to form a hydrogen bond with hydroxylic solvents even in the ground state. Hydrogen-bond formation in this case is a change in the direction of quaternization of the aza group, as demonstrated by spectral evidence.⁶⁷ Therefore, it is undoubtedly a rate-enhancing interaction.

1. Piperidino-Dechlorination at the Quinoline Ring

Illuminati and Marino^{29a} reported an interesting example of the dependence of solvent effects on the position of the reacting center relative to the aza group. The rate constants for the reaction of 2- and 4-chloroquinoline with piperidine were compared in three different solvents, methanol, piperidine, and toluene. These data are reported in Table III. Three main points are apparent from these data: (a) the different response of the two substrates to the action of the solvent, (b) the rates for 2-chloroquinoline in the three solvents tend to cluster around the highest reactivity level shown by 4-chloroquinoline in

⁶³ G. C. Finger and L. D. Starr, *J. Am. Chem. Soc.* **81**, 2674 (1959).

⁶⁴ H. Schroeder, *J. Am. Chem. Soc.* **82**, 4115 (1960).

⁶⁵ J. Miller and A. J. Parker, *J. Am. Chem. Soc.* **83**, 117 (1961). *Added in proof:* See, however, R. Bolton, J. Miller, and A. J. Parker, *Chem. Ind. (London)* 492 (1963).

⁶⁶ W. Gordy and S. C. Stanford, *J. Am. Chem. Soc.* **62**, 497 (1940); M. L. Josien, P. Dizabo, and P. Saumagne, *Bull. Soc. Chim. France* 423 (1957); G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," p. 201. Freeman, San Francisco, 1960.

⁶⁷ H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," p. 361. Wiley, New York, 1962.

methanol, and (c) the $\alpha:\gamma$ ratio varies markedly with the solvent type. The reactivity ratio for 4-chloroquinoline in the above-mentioned solvents is 1100:35:1, respectively, i.e., in the same direction as that expected from the solvating capacities of those solvents on both an acidity and a polarity basis. The latter property is also likely to play a role since the reaction involves neutral reactants and a charged transition state. In contrast to this, the reactivity of 2-chloroquinoline is much less sensitive to the nature of the solvent, the reactivity ratio here being 6.3:7.6:1, respectively. In methanol, 2-chloroquinoline is

TABLE III
SOLVENT EFFECTS ON THE PIPERIDINO-DECHLORINATION
OF CHLOROQUINOLINES^a

Solvent	Substituted quinoline		
	2-Chloro	4-Chloro	4-Chloro-7-nitro
Toluene	0.041	too slow	0.025
Piperidine	0.31	0.0091	0.86
Methanol	0.26	0.29	—

^a 104k (liter \times mole⁻¹ \times sec⁻¹), at 86.5°. Data from ref. 29a.

slightly less reactive than 4-chloroquinoline; in piperidine, 2-chloroquinoline is much more reactive than its 4-isomer. Correspondingly, the $\alpha:\gamma$ ratio increases from 0.9 to 34. The behavior of 2-chloroquinoline is apparently quite peculiar and must imply a specific *alpha*-effect of some kind. The above situation is qualitatively similar to that found in nitro-activated halogeno-aromatic compounds, i.e., the relative insensitivity to solvent changes of *o*-nitrochlorobenzene in comparison to the *p*-isomer and the trend of the *ortho*:*para* reactivity ratios.^{57, 68-71} To explain these solvent effects in the latter systems, Bunnett and Morath⁷² proposed the concept of "built-in" solvation. For reaction

⁶⁸ W. Greizerstein and J. A. Brieux, *J. Am. Chem. Soc.* **84**, 1032 (1962).

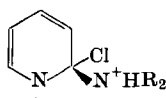
⁶⁹ N. B. Chapman, R. E. Parker, and P. W. Soanes, *J. Chem. Soc.* 2109 (1954).

⁷⁰ J. Miller and V. A. Williams, *J. Chem. Soc.* 1475 (1953).

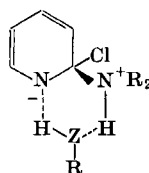
⁷¹ Data related to the piperidino-dechlorination of *o*- and *p*-nitrobenzene derivatives appear in refs. 57 and 68 for the reactions in non-polar solvents and in refs. 69 and 70 for the reactions in alcohols.

⁷² J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.* **77**, 5051, 5055 (1955).

with anionic nucleophiles, an electrostatic repulsive interaction between the reagent and the peripheral atoms of the activating group (NO_2 , CO_2^-) develops on the approach of the reagent at the *ortho*-position, tending to give the reactivity order *para* > *ortho*. In the case of neutral nucleophiles, the opposite situation arises in which a zwitterionic system is formed as the electronic charge flows from the initially neutral reagent to the activating group. When the attack is *ortho*, appreciable electrostatic attraction occurs, and solvation in the ordinary sense ("external" solvation) is reduced by extensive neutralization of opposed-charge polarities facing each other ("built-in" solvation). The latter implies little dependence on the solvent. In the reaction of 2-chloroquinoline, the relatively small kinetic factor involved on changing the solvent from methanol to toluene (6.4 at 86.5°) is entirely accounted for by the 1.4 kcal/mole difference in the energy of activation. In both solvents the entropy of activation is -35 ± 0.1 eu. "Built-in" solvation in aza-activated systems may arise from either structure **13** or **14**. If solvent hydrogen bonding occurs in



[13]



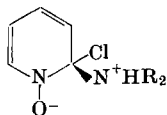
[14]

the rate-determining step, the geometry of the system requires, for formation of a six-membered ring to be possible, an extra molecule from the medium, which can be either a molecule of the solvent ($\text{Z} = \text{O}$) or a second molecule of the reagent ($\text{Z} = \text{NR}$). The latter case warrants a reaction order higher than one, with respect to the nucleophile, under inert solvent conditions. This point has not as yet been tested experimentally for the reaction discussed above (see, however, Section II, D, 2, b).

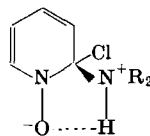
2. The Behavior of *N*-Oxides

A general solvent dependence of the $\alpha:\gamma$ ratio similar to that noted above is also probable for piperidino-dehalogenation of *N*-oxides. 4-Bromoquinoline and its *N*-oxide show a strong and nearly identical dependence on the nature of the solvent,³² the rate increases on going from benzene to 95% ethanol, being in the order of 10^2 at 120° .

Furthermore, the relatively high reactivity of 2-chloropyridine *N*-oxide as compared to that of the 4-isomer and the detailed inconsistency with theoretical parameters have also been explained in terms of "built-in" solvation *via* either direct electrostatic interaction or hydrogen bonding⁷³ (structures **15** and **16**, respectively).



[15]

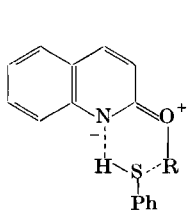


[16]

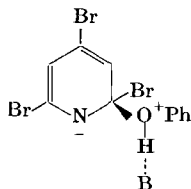
3. The Scope of Specific *alpha*-Effects

A careful use of solvent effects should be of great assistance in synthetic chemistry. For example, it may be predicted from the solvent effects described above that in the reaction of 2,4-dichloroquinoline with piperidine the $\alpha:\gamma$ ratio should increase in the less polar solvents, although the result might be obscured by the mutual influence of the two chlorine substituents. Nitro-activated benzenes support this prediction since *ortho*:*para* ratios of 4.2 in methanol and 69 in benzene were observed in the reaction of 2,4-dichloronitrobenzene with piperidine.⁶⁸

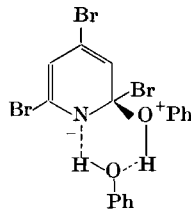
Examples from preparative chemistry indicate the possible occurrence of special *alpha*-effects in several other cases. The different reaction of 2- and 4-ethoxyquinolines with a thiol yielding carbostyryl and a 4-arylthio derivative, respectively,⁷⁴ may indicate the intervention of structures such as **17** in the transition state of the 2-isomer.



[17]



[18]



[19]

⁷³ G. Coppens, F. Declerk, C. Gillet, and J. Nasielski, *Bull. Soc. Chim. Belges* **70**, 480 (1961).

⁷⁴ G. Illuminati and H. Gilman, *J. Am. Chem. Soc.* **71**, 3349 (1949).

The predominance of α -substituted products in the reaction of 2,4,6-tribromopyridine in phenol solution⁶¹ may result from competitive attack by free phenol in preference to attack by the phenoxide ion reagent involving structures **18** (B = base) or **19**. A wealth of chemistry awaits elucidation by physical-organic studies.

C. METHOXIDE ION, ARYLSULFIDE IONS, AND OTHER CHARGED REAGENTS

Among the charged reagents, methoxide and phenylsulfide ions are of special interest since their relative reactivities in methanol are usually in the reverse order to their basicities.⁷⁵ With the exception of *p*-nitrofluorobenzene,⁷⁶ toward which the two reagents are equally reactive, the phenylsulfide ion is generally much more reactive with nitro-activated halogenobenzenes.⁷⁷ Another important feature of both of these reagents is the greater reactivity of *p*-chloronitrobenzene compared to the *ortho* isomer.⁷⁸ Recent work by Illuminati and Marino^{29b} has disclosed new features on the relative reactivity of these anionic reagents in connection with aza-activated substrates. The pertinent rate data are reported in Table IV for 2- and 4-chloroquinoline.

TABLE IV
A COMPARISON OF THE REACTIVITIES OF CHLORO-
QUINOLINES WITH METHOXIDE AND ARYLSULFIDE
REAGENTS^a

Substrate	CH ₃ O ⁻	<i>p</i> -MeC ₆ H ₄ S ⁻	$k_{\text{ArS}^-}/k_{\text{RO}^-}$
2-Chloro	6.73	1.68	0.24
4-Chloro	6.30	16.04	2.50

^a 10⁴*k* (liter \times mole⁻¹ \times sec⁻¹); reactions in methanol at 86.5°. Data from ref. 29b.

⁷⁵ J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.* **76**, 3011 (1954).

⁷⁶ C. W. L. Bevan and J. Hirst, *J. Chem. Soc.* 254 (1956).

⁷⁷ J. F. Bunnett and W. D. Merritt, Jr., *J. Am. Chem. Soc.* **79**, 5967 (1957).

⁷⁸ J. F. Bunnett and R. F. Snipes, *J. Am. Chem. Soc.* **77**, 5422 (1955).

Like the chloronitrobenzenes, a chloroquinoline reacts faster with sodium *p*-tolylsulfide when the chloro group is *para* to the aza-group than when it is *ortho*, the factor involved being about 10. However, a strikingly different behavior is noted in the much lower $k_{\text{RS}^-}/k_{\text{RO}^-}$ ratio which is 2.5 for 4-chloroquinoline ("para" isomer) and 0.24 for 2-chloroquinoline ("ortho" isomer). For *p*-chloronitrobenzene⁷⁷ this ratio is 38, and for 2,4-dinitrochlorobenzene it is 1950. Thus far there is no case in which the reaction of a chloronitrobenzene derivative with sodium methoxide is faster than that with sodium phenylsulfide.

From the above data, it is apparent that the $k_{\text{RS}^-}/k_{\text{RO}^-}$ ratio strongly depends on the aromatic substrate. In particular, it depends not only on the degree of activation of the substrate and on the displaced group⁷⁷ but probably also on the type of activation.

On both experimental^{56, 77} and theoretical grounds^{55c} there is little doubt of the importance of polarizability as a major factor in determining the commonly encountered, though variable, high RS^-/RO^- ratios. Were thermodynamic carbon affinities mainly responsible⁷⁹ for the usual reactivity order $\text{RS}^- > \text{RO}^-$, the peculiar behavior of chloroquinolines would be very difficult to understand. There is some indication, however, that carbon affinities roughly parallel basicities (hydrogen affinities).⁸⁰ In the latter case, lower RS^-/RO^- ratios could be explained in terms of the intermediate complex mechanism.^{80a}

It may be unsafe to carry this discussion further until more data are available. Knowledge of the activation parameters would be especially desirable in several respects. Reactivity orders involving different reagents or substrates may be markedly dependent on temperature. Thus, in Table IV both 2- and 4-chloroquinolines appear to be about equally reactive toward sodium methoxide at 86.5°. However, the activation energies differ by 3 kcal/mole (see Section VII), and the relative rates are reversed below and above that temperature. Clearly, such relative rates affect the $k_{\text{RS}^-}/k_{\text{RO}^-}$ ratios.

Low RS^-/RO^- reactivity ratios are also found in systems other than six-membered ring *N*-heterocycles. Thus, for 2-chlorobenzothiazole⁸¹ the ratio is 0.36. Moreover, the above-discussed dependence of the

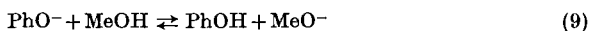
⁷⁹ B. Miller, *Proc. Chem. Soc.* 303 (1962).

⁸⁰ (a) J. F. Bunnett, C. F. Hauser, and K. V. Nahabedian, *Proc. Chem. Soc.* 305 (1961); (b) A. J. Parker, *ibid.* 371 (1961).

⁸¹ P. E. Todesco and P. V. Vivarelli, *Boll. Sci. Fac. Chim. Ind. Bologna* 20, 143 (1962).

RS⁻/RO⁻ ratio on the degree and type of activation is further confirmed in the latter system where the presence of a 6-nitro substituent increases the ratio to 1.8 or higher.

A more proper comparison regarding VI-group nucleophilic reagents would be between the pairs PhO⁻ and PhS⁻, and MeO⁻ and MeS⁻. However, both phenoxide and alkylsulfide ions are more basic than phenylsulfide ion, and their reactions are less amenable to study in alcoholic solution. For dilute solutions of phenoxide in methanol the equilibrium (9) shifts nearly half-way toward the right⁸² if a stoichiometric excess of phenol is not present. If phenoxide ion is less reactive



than methoxide ion towards chloroheteroaromatic compounds, as it is with nitroactivated chlorobenzene derivatives,^{75, 83} the reaction of MeO⁻ should predominate over that of PhO⁻ unless a sufficient excess of initially added free phenol is present. In agreement, gas-chromatographic analysis showed, in a kinetic study, that sodium phenoxide did not react with 2-chloroquinoline in methanol and that only the methoxy derivative was formed. With aza-activated systems, addition of free phenol is likely to lead to acid-catalyzed reactions.⁸⁴

D. OTHER REAGENT AND SOLVENT EFFECTS

The relative effects of methanol and ethanol as solvents in the reaction of 2-chloro-5-nitropyridine with aniline can be deduced from recent data by Chapman *et al.*^{26, 47} and are reported in Table V. These alcohols differ appreciably in their polarity and acidity. Although the activation energies differ by more than 1 kcal/mole, the reaction rates for the above compounds are almost identical, indicating that opposing factors nearly balance each other. The effect of stronger hydrogen-bond solvation of the reagent in methanol is probably counterbalanced by the higher polarity of this solvent.

The rate data³⁶ reported in Table VI can be interpreted with less certainty in terms of solvent effects, since for each alcohol tested the

⁸² B. D. England, *Chem. Ind. (London)* 1145 (1954); see also, J. W. Baker and A. J. Neale, *Nature* **172**, 583 (1953).

⁸³ G. D. Leahy, M. Liveris, J. Miller, and A. J. Parker, *Australian J. Chem.* **9**, 382 (1956).

⁸⁴ See ref. 29b. A detailed study of these systems involving VI-group nucleophilic reagents is in progress in the author's laboratory.

TABLE V
THE ALCOHOL EFFECT IN THE ANILINO-DECHLORINATION OF
2-CHLORO-5-NITROPYRIDINE^a

Solvent	10^5k (liter \times mole ⁻¹ \times sec ⁻¹), at 50°	E(kcal/mole)
Ethanol, 99.8%	0.79	13.1
Methanol	0.93	14.9

^a Data from refs. 26 and 47.

nucleophilic reagent is itself changed. Clearly the reaction rates are not controlled by polarity (ϵ) alone, since butanol reacts markedly faster than the slightly more polar isopropanol. The rates decrease in the order expected from the acidity (K_a)⁸⁵ and steric requirements of the attacking alcohol. Probably both the latter properties contribute to the observed rates.

TABLE VI
PSEUDO-FIRST-ORDER RATES FOR THE SOLVOLYSIS OF
CYANURIC CHLORIDE IN VARIOUS ALCOHOLS^a

Solvent	$10^4 \times k$ (min ⁻¹), at 15°	ϵ (25°)	K_a
Methanol	230	32.6	4.0
Ethanol	79	24.3	0.95
<i>n</i> -Butanol	57	17.1	0.6
Isopropanol	8	18.3	0.08

^a Data from refs. 36 and 85.

Still more difficult to interpret are the rates of reactions of the several alkoxides in their respective alcohols,⁸⁶ since in this case strong anion-solvent interactions are involved. We may only note that a series of alcohols including a fairly large variety of structural types (straight-

⁸⁵ J. Hine and M. Hine, *J. Am. Chem. Soc.* **74**, 5266 (1952).

⁸⁶ R. J. Petfield, Ph.D. Thesis, Lehigh University, Bethlehem, Pa., 1959; *Dissertation Abstr.* **20**, 1589 (1959).

chain, saturated, unsaturated, cyclic) show maximum kinetic differences corresponding to a rate factor of 5.2 and to changes in energy and entropy of activation of 2 kcal/mole and 5 eu, respectively.

Finally, these reactions do not seem to be appreciably dependent on the structure of the substrate since methoxy- and ethoxy-dehalogenation in their respective alcohols proceed at nearly the same rate with each of the substrates, 2- and 4-chloroquinoline^{20, 87} and 2-bromopyridine.⁸⁶

IV. The Reactivity of the Heterocyclic Substrate

Although the susceptibility to catalytic phenomena due to the presence of the basic ring-nitrogen atom seriously interferes with the study of structural effects of the substrate on reactivity, complications of this kind are found only for neutral nucleophilic reagents of the general type RZH (Z = O, S, NH, NR') and not for anionic reagents (alkoxide, etc.). Even with the former reagents, conditions can be found for many substrates where the obscuring effects of autocatalysis are avoided. However, as is shown in Section II, D, it is difficult *a priori* to define the precise boundaries of autocatalysis. Many preparative results could be misleading if used to interpret the effects of substituents. Knowledge of the kinetic course of the reaction is essential in deciding its suitability for structural correlation.

In this Section the available data will be arranged according to the following main points of interest: magnitude of activation of the heteroaromatic system, substituent effects, and leaving-group effects. In order to present some of the data and to compare reaction rates from different laboratories it was often necessary to calculate the rate constants at a given temperature, and this was done by replotting the Arrhenius diagrams to minimize possible errors. Comparing reaction rates at a given temperature for compounds of widely different reactivities calls for certain reservations, since rate ratios depend appreciably on temperature. This is especially true for any two compounds not differing by a systematic change such as that relating the several members of a structural series in which an empirical correlation with the free energy of activation is generally to be found. The temperature at which the rates of any two such compounds should be compared may be difficult to determine on theoretical grounds⁸⁸; from the

⁸⁷ M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron* **19**, 345 (1963).

⁸⁸ J. E. Leffler, *J. Org. Chem.* **20**, 1202 (1955).

practical point of view we should know their relative reaction rates at temperatures not too far from those at which each of the compounds can be actually measured. Attempting to normalize all the data in the literature would require extensive recalculations and would exceed the scope of this Section. However, this practical criterion has been used whenever such calculations were required in the tables.

A. THE ACTIVATING POWER OF THE AZA GROUP

In this subsection the relative rate data are surveyed to give a general picture of aza-activation in its various aspects.

1. Activation Relative to an Aromatic "CH" Group

Pertinent data are contained in Table VII. Only a few examples in this table refer to non-activated systems as the reference substrates, i.e., the 2-halogenonaphthalenes^{18, 20, 89}; these are more accessible for kinetic studies than the halogenobenzenes and follow "normal" substitution under the conditions reported. The other data concern insertion of an aza group into a nitro-^{42, 69} or an aza-activated substrate.^{18, 20, 29, 43}

There are only two values for the effect of a *para*-aza group: both are of the order of 10^7 .^{20, 43}

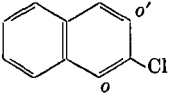
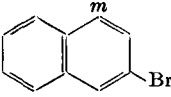
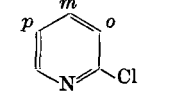
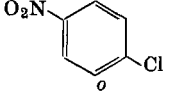
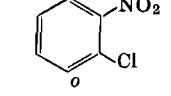
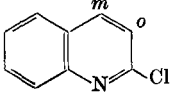
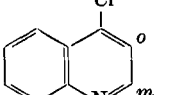
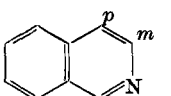
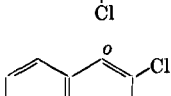
As to the *ortho*- and *meta*-aza groups, the several values reported cover a very wide range of activation involving factors in the ranges of 3×10^3 to 7×10^9 , and 4 to 1×10^4 , respectively. In *ortho*-activation the chemical non-equivalence of the *o,o'*-positions of 2-chloronaphthalene is striking, since the activating power of the *o*-aza group (2-chloroquinoline) exceeds that of the *o'*-aza group (3-chloroisoquinoline) by a factor greater than 10^4 .

The aza-effects at all positions are available only for 2-chloropyridine, and these show the reactivity sequence $p > o \gg m$.

The incompleteness of the other data precludes generalization. However, a few apparent inconsistencies may be indicated to stimulate further research. Insertion of another aza group into 2-chloroquinoline causes the reactivity sequence $o > m$ (reaction with piperidine) or, even, $o < m$ (reaction with $C_2H_5O^-$), involving only relatively small factors and, in any case, in sharp contrast with the above-mentioned effects on 2-chloropyridine as a substrate. Further, *meta*-aza activation in all cases involving the ethoxide ion is fairly strong suggest-

⁸⁹ K. R. Brower and E. D. Amstutz, *J. Org. Chem.* **18**, 1075 (1953).

TABLE VII
THE MAGNITUDE OF AZA-ACTIVATION RELATIVE TO THE AROMATIC "CH"
GROUP

Reference substrate	Rate of the aza-derivative relative to the reference substrate			Reference
	<i>ortho</i>	<i>meta</i>	<i>para</i>	
	$6.9 \times 10^9 (o)^a$ $1.3 \times 10^5 (o')^a$	— —	— —	20
	—	4.4^b	—	18, 89
	$6.9 \times 10^5^c$ $7.4 \times 10^5^a$	43^d —	1.5×10^{7e} —	20, 43
	1.3×10^{4e}	—	—	42, 69
	3.3×10^{3e}	—	—	42, 69
	4.7×10^{3a} 3.2×10^{3c}	1.3×10^{4a} 4.2×10^{2c} 14^f	— —	18, 20, 43
	2.2×10^{6g}	7.3×10^{3a}	—	20, 29, 43
	— —	80^c 2.7×10^{3a}	1.2×10^{7e} —	20, 43
	2.5×10^{8a}	—	—	20

ing a marked inductive effect of the aza group,¹⁸ which is confirmed in substituent effect studies (see Section IV, C, 1, d). However, the *m*-aza-activating power with piperidine as the reagent is in nearly all cases very modest, involving factors as low as 14 at 75.2° or 4 at 201°. These results are in contrast to the indications that hetero-aromatic substitutions tend to be equally highly selective (see Section IV, C, 1, b and IV, C, 2) with different reagent types.

2. Relative Activating Power of Nitro and Aza Groups

It is now of interest to compare the activation by the aza group with that by the well-known nitro group. A number of examples^{19, 20, 26, 69, 70, 90-92} are reported in Table VIII. In substantial agreement with Mangini and Frenguelli's early study,⁹³ the relative rates, NO₂/aza, generally involve factors within one order of magnitude, which is a small difference compared with the very high reactivity relative to an aromatic "CH" group. Thus, it should not be too surprising if the reactivity order NO₂ > aza is (at the *para* position) reversed in some cases.

A number of factors may operate in determining the relative rates. The consistently higher reactivity of the nitro compound with charged reagents may indicate a somewhat higher capacity of the nitro group to accommodate the electronic charge in the transition state, whereas the conflicting behavior observed at the *ortho* and *para* positions for neutral reagents may result from a combination of solvent and hydrogen-bonding effects (see Section III) which obscure the fundamental structural differences between the two activating moieties.

⁹⁰ C. W. L. Bevan, *J. Chem. Soc.* 2340 (1951).

⁹¹ M. Simonetta and G. Favini, *Atti. Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **16**, 84 (1954).

⁹² G. Illuminati and F. Tarli, *Ric. Sci.* **28**, 1464 (1958).

⁹³ A. Mangini and B. Frenguelli, *Gazz. Chim. Ital.* **69**, 86 (1939).

^a C₂H₅O⁻ at 20°.

^b Piperidine in piperidine at 201°.

^c Piperidine in ethanol at 20°.

^d Piperidine in weakly polar solvents at 75.2°. The solvent was piperidine for 2-chloropyridine and toluene for 2-chloropyrazine; the comparison is not correct but is justified by evidence given in Section III.

^e Piperidine in ethanol at 90°.

^f Piperidine in toluene at 75.2°.

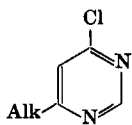
^g Piperidine in alcohol at 86.5°. The solvent was methanol for 4-chloroquinoline and ethanol for 4-chloroquinazoline.

TABLE VIII
RELATIVE ACTIVATING POWER OF NITRO AND AZA GROUPS

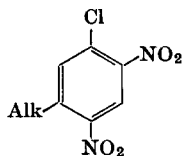
Nitro compound	Aza compound	Conditions	Relative rate, NO ₂ /aza	Reference
1-Cl-2-NO ₂ -benzene	2-Cl-pyridine	Piperidine in EtOH, 90°	76.5 (<i>ortho</i>)	20, 69
2-Cl-3-NO ₂ -pyridine	2-Cl-pyrimidine	Piperidine in EtOH, 30°	6.5 (<i>ortho</i>)	42
2-Cl-4-CH ₃ -5-NO ₂ -pyridine	4-Cl-6-CH ₃ -pyrimidine	Piperidine in EtOH, 30°	0.59 (<i>para</i>)	42
1-Cl-2,4-(NO ₂) ₂ -benzene	2-Cl-5-NO ₂ -pyridine	Pyridine in EtOH, 55°	5.6 (<i>ortho</i>)	26
1-Cl-2,4-(NO ₂) ₂ -benzene	4-Cl-3-NO ₂ -pyridine	Pyridine in EtOH, 55°	0.35 (<i>para</i>)	26
1-Cl-2,4-(NO ₂) ₂ -benzene	2-Cl-5-NO ₂ -pyridine	Aniline in EtOH, 55°	30 (<i>ortho</i>)	26
1-Cl-2-NO ₂ -benzene (MeO ⁻)	2-Cl-pyridine (EtO ⁻)	"Alkoxide" in alcohol, 90°	10 (<i>ortho</i>)	20, 70
1-Cl-4-NO ₂ -benzene	4-Cl-pyridine	EtO ⁻ in EtOH, 60°	15.1 (<i>para</i>)	20, 90
1-Cl-4-NO ₂ -naphthalene	4-Cl-quinoline	EtO ⁻ in EtOH, 60°	8.4 (<i>para</i>)	20, 91
1-Cl-4-NO ₂ -naphthalene	4-Cl-quinoline	MeO ⁻ in MeOH, 60°	6.3 (<i>para</i>)	19, 92

From the standpoint of geometrical considerations, the major difference is in the far greater steric requirements of the nitro group. This could result in either primary or secondary steric effects. Nevertheless, primary steric effects do not seem to be necessarily distinguishable by direct kinetic comparison. A classic example is the puzzling similarity of the activation parameters of 2-chloropyrimidine and 2,6-dinitrochlorobenzene (reaction with piperidine in ethanol), which has been described by Chapman and Rees⁴² as fortuitous. However, that nitro groups do cause (retarding) primary steric effects has been neatly shown at *peri* positions in the reaction with alkoxides (see Section IV, C, 1, c).

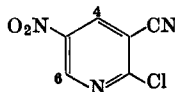
Secondary steric effects of nitro groups are more easily detected by comparing the reactivities with those of aza derivatives. For example, in structure **20** the rate depression on passing from methyl to *t*-butyl is only 2.5-fold and can be attributed to an inductive effect, whereas in structure **21** a similar change involves the factor 16, which can be attributed in part to steric inhibition of resonance (S.I.R.) of the *p*-NO₂ group⁹⁴ (reaction with piperidine).



[20]



[21]



[22]

Secondary steric effects of the same kind have been found in the reaction of methyl derivatives of **22** with aniline. A methyl group at position 6 has a 4-fold rate-diminishing effect (mainly inductive), but when positions 4 and 6 are both methylated the effect is 81-fold and is mainly of steric origin.⁴⁷

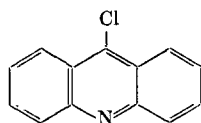
In all these cases the S.I.R. effect has a greater influence on the energy than on the entropy of activation (see Section VII).

The steeply increasing steric compression shown when passing from one to two adjacent methyl groups⁹⁵ is dramatically illustrated in the case of *peri*-hydrogens. Annulation of a benzo ring has the usual rate-increasing effect (see Section IV, C, 4), i.e., on going from 4-chloro-

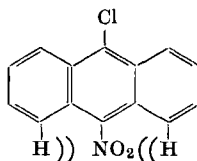
⁹⁴ S. Capon and N. B. Chapman, *J. Chem. Soc.* 600 (1957).

⁹⁵ P. Van Berk, J. O. M. Van Langen, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.* **75**, 1137 (1956).

pyridine to 9-chloroacridine (formula **23**); rate-enhancement is also observed on going from *p*-chloronitrobenzene to 1-chloro-4-nitronaphthalene, but *not* from here to 9-chloro-10-nitroanthracene (**24**).^{92, 96} The rate-depression due to the two *peri*-hydrogen atoms involves a factor of about 10^2 .



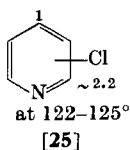
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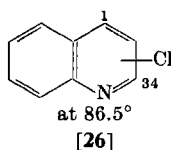
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3. Activation at Non-Equivalent Positions

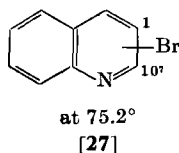
In principle, this aspect of the reactivity of aza-activated compounds might be deduced from data of the kind shown in Table VII, but experimentally it is easier to obtain by direct comparison of the mobilities of the leaving group from the non-equivalent positions of a given



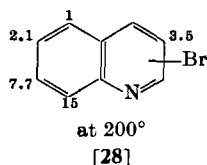
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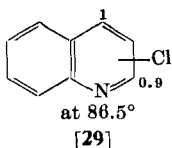
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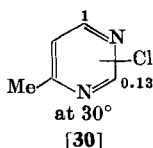
[27]



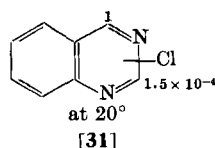
[28]



[29]



[30]

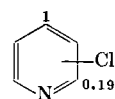


[31]

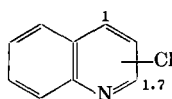
CHART 1. Experimental reactivity diagrams from piperidino-dehalogenation. Rates relative to a given position (= 1). Reactions in piperidine, structures **25-28**; in alcohol, structures **29-31**. Data deduced from refs. 18, 20, 29, 42, 43 and 98.

⁹⁶ G. Illuminati, G. Marino, and O. Piovesana, *Ric. Sci.*, in press (1964).

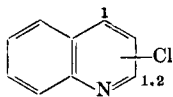
aza-containing substrate. The problem has considerable theoretical interest, since the substrates involved can be treated by the approximation methods of quantum mechanics and this offers opportunities of testing quantitative correlations of theoretical parameters such as charge density, bond-orders, and localization energies with experimental reactivities.⁹⁷ Therefore, the pertinent experimental data on this subject will be summarized. One aspect of the problem concerning $\alpha:\gamma$ ratios is dealt with in Section III, where it is shown that in the reaction with neutral reagents, $\alpha:\gamma$ ratios are strongly subject to solvent effects. Additional data (Charts 1 and 2) show in a self-explanatory form the change in reactivity resulting from the presence of leaving groups in non-equivalent positions.

EtO⁻ at 90°

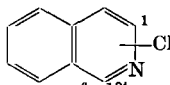
[32]

EtO⁻ at 70°

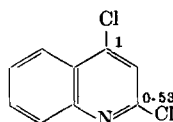
[33]

MeO⁻ at 90°

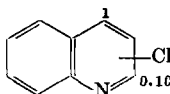
[34]

EtO⁻ at 20°

[35]

MeO⁻ at 75.2°

[36]

ArS⁻ at 86.5°

[37]

CHART 2. Experimental reactivity diagrams for charged reagents. Rates relative to a given position (= 1). Data deduced from refs. 20, 29, and 99.

Relative reactivities at non-equivalent positions are a function of the structure of the substrate as well as of the reagent type, which should be allowed for in the theoretical treatment.

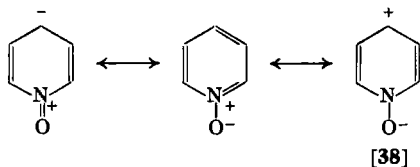
⁹⁷ H. C. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.* 971 (1949).

⁹⁸ T. E. Young and E. D. Amstutz, *J. Am. Chem. Soc.* **73**, 4773 (1951).

⁹⁹ G. Marino, *Ric. Sci.* **30**, 2094 (1960).

B. THE ACTIVATING POWER OF THE *N*-OXIDE GROUP

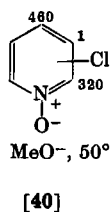
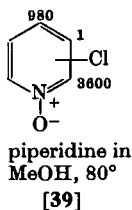
The *N*-oxide group is more strongly activating in nucleophilic substitution than the aza group itself because of the increased contribution of the polarized structure **38**.¹⁰⁰



Okamoto *et al.*³² found that *N*-oxidation activates 4-halogenoquinolines in the reaction with piperidine in aqueous alcohol by kinetic factors of 9 to 25, at 100°. This rate-enhancing effect is accompanied by a fairly large decrease in the enthalpy of activation (up to 10 kcal/mole in the chloro compounds), the effect of which is partly offset by a decrease in the entropy of activation.

A similar kinetic effect was reported for the reaction of 4-chloropyridine 1-oxide with methoxide ion at 50°, and still larger effects were obtained with the 2- and 3-isomers at the same temperature.²¹

The β -position of pyridine 1-oxide is much less reactive than either the α - or γ -position. This is shown for the displacement of the chloro group in structures **39** and **40**; the relative rates are indicated ($\beta = 1$) at



the appropriate positions according to recent work by Coppens *et al.*⁷³ and by Boxer.²¹ The α - and γ -positions are of comparable reactivity in the reactions compared in the above diagrams, although the order is inverted in the two reactions. As mentioned in Section III, B, 2, the order, $\alpha > \gamma$, for the piperidine reaction has been attributed to "built-in" solvation.

¹⁰⁰ E. P. Linton, *J. Am. Chem. Soc.* **62**, 1945 (1940); A. R. Katritzky, E. W. Randall, and L. E. Sutton, *J. Chem. Soc.* 1769 (1957).

C. SUBSTITUENT EFFECTS

1. Substituent Effects in the Aza-Naphthalene Ring

a. *Alkoxy-Dechlorination*. Mainly for reasons of synthetic accessibility, studies of substituent effects on homoaromatic reactivity have developed unevenly with the emphasis being placed on nitrobenzene rather than nitronaphthalene derivatives. For similar reasons, a contrary development has occurred in studies of heteroaromatic reactivity which have been concerned less with aza-benzene than with aza-naphthalene derivatives. Therefore, the latter systems are considered first in the hope that the more fragmentary data on the aza-benzene compounds might then be presented on a somewhat firmer basis.

Aza-naphthalene compounds offer a variety of positions in addition to the familiar *ortho*, *meta*, and *para* positions. According to Erdmann,¹⁰¹ the new positions may be named similarly as *cata*, *amphi*, *ana*, *epi*, *pros*, and *peri* on the basis of their effective structural

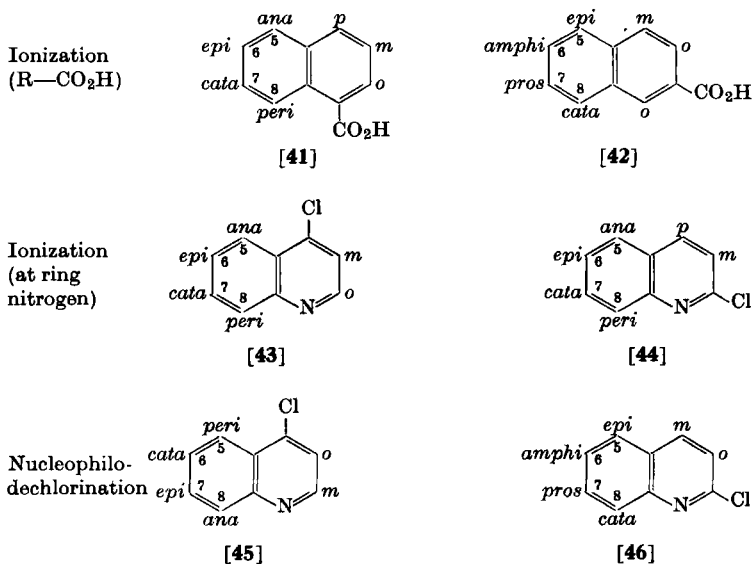


CHART 3. Examples of Erdmann's system of nomenclature.

¹⁰¹ See, for example, V. Grignard, "Traité de Chimie Organique," Vol. XVII (I). Masson, Paris, 1949; H. Erdmann, *Ann. Chem.* **275**, 184 (1893).

relationship. They fall into two classes, depending on whether conjugation with the point of attachment of the reagent is possible (the first three), in analogy with the *ortho* and *para* positions, or whether it is not possible (the last three), in analogy with the *meta* position. In the

TABLE IX
RELATIVE RATES FOR THE METHOXY-DECHLORINATION OF
4-CHLOROQUINOLINES AT 75.2°^a

Substituent	k/k_0	Substituent	k/k_0
None	1	6-Ethoxy	0.191
2-Methyl	0.314	2-Methylthio	0.474
6-Methyl	0.387	6-Methylthio	1.230
2-Trifluoromethyl	67.9	7- <i>p</i> -Tolylthio	2.38
6-Dimethylamino	0.0292	6-Fluoro	2.13
5-Nitro	7.250	7-Fluoro	5.00
6-Nitro	428	2-Chloro	30.2
7-Nitro	104	6-Chloro	6.80
2-Methoxy	0.0579	7-Chloro	8.68
6-Methoxy	0.214	6-Bromo	8.67
7-Methoxy	0.583	7-Bromo	8.81
2-Ethoxy	0.0644	2-Aza	1200

^a Data from refs. 19, 87, and 103.

course of the structural studies carried out in this author's laboratory, adoption of Erdmann's system of nomenclature proved very useful and was less confusing than a ring-numbering system which is independent of the position of the reaction center. Indeed, the two systems do not parallel each other, as is illustrated in the few examples shown in Chart 3.

Extensions to other reactions and to other aza-naphthalene systems is obvious. The chemical equivalence between formally identical positions in all possible situations must be established experimentally. In this connection, caution should be used because for some of the above positions steric hindrance may become an important factor in determining the overall reactivity.

TABLE X
RELATIVE RATES FOR THE METHOXY-DECHLORINATION OF
2-CHLOROQUINOLINES AT 75.2°^a

Substituent	k/k_0	Substituent	k/k_0
None	1	4-Methoxy	0.219
4-Methyl	0.395	4-Ethoxy	0.215
7-Methyl	0.509	4-Methylthio	0.874
4-Cyano	536	4-Chloro	17.75
4-Acetyl	21.36	6-Chloro	6.21
4-Trifluoromethyl	136.2	7-Chloro	10.63
6-Nitro	807.6	4-Aza	2470

^a Data from refs. 87 and 104.

The effects of about 50 substituents have been examined by Illuminati, Marino, and their co-workers^{19, 87, 102-105} on the kinetics of the methoxy-dechlorination of 2- and 4-chloroquinoline, 2-chloro-quinoxaline, and 4-chlorocinnoline. The pertinent data are assembled in Tables IX to XI.

¹⁰² M. L. Belli, S. Fatutta, M. Forchiassin, G. Illuminati, P. Linda, G. Marino, and E. Zinato, *Ric. Sci.* **33** (II-A), 530 (1963).

¹⁰³ G. Bressan, A. Ciana, G. Illuminati, and G. Marino, *Ric. Sci.* **33** (II-A), 533 (1963); a more complete report of this kinetic work will appear in *J. Am. Chem. Soc.*

¹⁰⁴ G. Illuminati, P. Linda, G. Marino, and E. Zinato, *Ric. Sci.* **33** (II-A), 533 (1963); a more complete report of this kinetic work will appear in *J. Am. Chem. Soc.*

¹⁰⁵ G. Illuminati and G. Marino, *Atti Acad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **34**, 407 (1963).

In agreement with the assumption of a nucleophilic bimolecular reaction, increased electron deficiency at the site of the displacement causes acceleration and *vice versa*. The reaction is very sensitive to substituent effects, in accordance with what is found with nitrobenzene derivatives and what is generally expected for a nuclear

TABLE XI

RELATIVE RATES FOR THE METHOXY-DECHLORINATION OF
2-CHLOROQUINOXALINES AND 4-CHLOROCINNOLINES AT 5°^a

4-Chloroquinoxalines		4-Chlorocinnolines	
Substituent	k/k_0	Substituent	k/k_0
None	1	None	1
7-Methyl	0.433	7-Chloro	5.21
7-Trifluoromethyl	40.6		
6-Nitro	1170		
7-Nitro	175		
7-Methoxy	0.303		
6-Chloro	5.70		
7-Chloro	11.2		
7-Bromo	13.0		

^a Data from refs. 103 and 104.

substitution. Although in this reaction a fairly high degree of randomness in the changes in energy (or enthalpy) and entropy of activation exists, several correlations of the free-energy of activation with structure indicate that structural changes are most simply interpreted in terms of relative rates. This is in fact a commonly observed situation.¹⁰⁶

Two closely related series are 2-chloroquinoline and 2-chloroquinoxaline, and the 6- and 7-substituents in both series are of the

¹⁰⁶ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 255. Cornell University Press, Ithaca, 1953.

amphi and *pros* type, respectively. The correlation between reactivities is remarkably good (Fig. 2). The correlation coefficient (r) of this line is 0.999 and the slope is + 1.07. It should be noted that conjugative and inductive effects appear to be transmitted equally well through aromatic aza and CH groups.

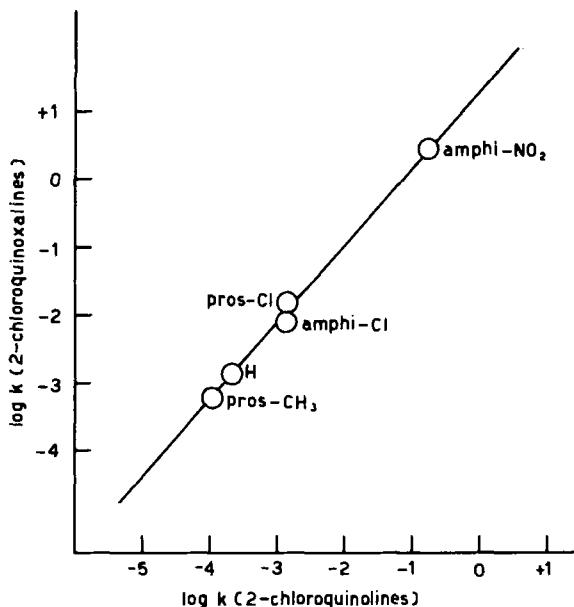


FIG. 2. Correlation of reactivity data ($\log k$) for the methoxy-dechlorination of substituted 2-chloroquinolines and 2-chloroquinoxalines.

In view of the importance of *meta* substituents in the assessment of substituent effects through the evaluation of reaction constants (see Section IV, C, 1, d), special attention was paid to a comparison of the *meta* positions of 2- and 4-chloroquinoline. The transmissions of electrical effects from these positions approximately parallel each other (cf. Fig. 3). The slope of this line is + 1.04. The observed scattering about this line could well be caused by a number of disturbances, including proximity effects, when the substituent or the leaving group is located *alpha* to the aza group, and secondary steric effects, when the substituent is *peri* to the 5-hydrogen atom. Thus, despite the essential applicability of the above correlation, the scattering of the points reflects an irregular behavior of the relative reactivities of the 2- and

4-positions of quinoline. For example, a *m*-OCH₃ group decreases the reaction rate of 4-chloroquinoline ($k/k_0 = 0.06$) more than that of the 2-chloro isomer ($k/k_0 = 0.22$), whereas a *m*-trifluoromethyl group is less rate-enhancing in the former ($k/k_0 = 68$) than in the latter isomer ($k/k_0 = 140$); this is inconsistent with a strictly linear dependence.

Epi and *cata* substituents show a linear correlation between nucleophilic reactivity of 4-chloroquinoline and basicity⁷ (reaction

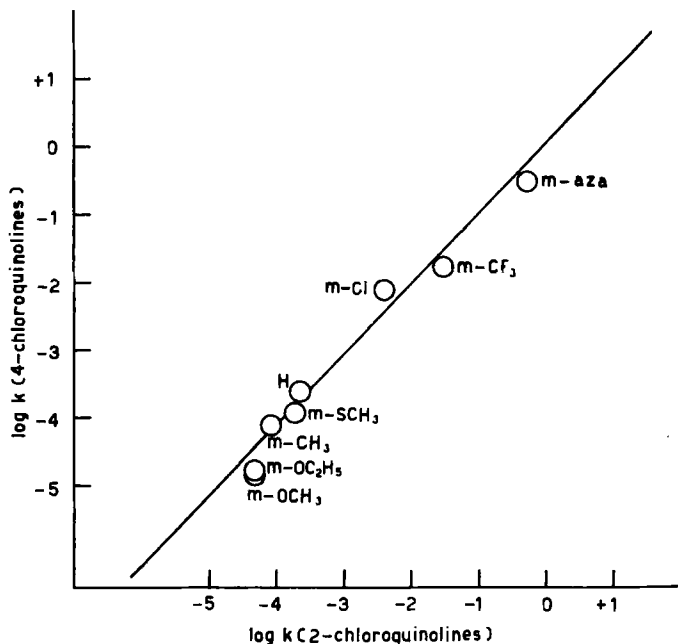


FIG. 3. Correlation of reactivity data ($\log k$) for the methoxy-dechlorination of *meta*-substituted 2- and 4-chloroquinolines.

III of Chart 3), as is shown in Fig. 4. This is of interest because both of these reactions involve direct attack on the ring and, in spite of the fact that they are of widely different types, they are both highly selective. The correlation, however, is limited to alkoxy, methyl, and halogeno groups, but its value would certainly be increased by extension to other substituent types.

Finally, the available data allow two further correlations involving "benzoic" and "naphthoic" reactivities. These are shown in Figs. 5 and 6 and are discussed later.

A few comments on the polar effects of the substituents reported in Tables IX–XI are now relevant. With the exception of 4-chloro-5-nitroquinoline (see Section IV, C, I, c), they involve only positions not subject to primary steric effects. The relations to the reaction center are of the conjugative (*cata*, *amphi*) as well as of the non-conjugative class (*meta*, *epi*, *pros*) as shown in Chart 3 by structures 45 and 46.

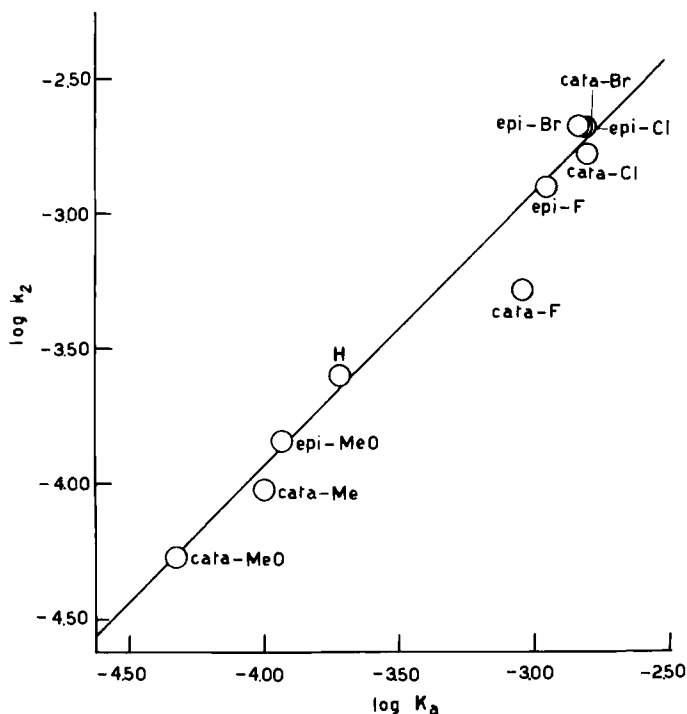


FIG. 4. Correlation of rate data ($\log k_2$) for methoxy-dechlorination with basicity data ($\log K_a$) for some substituted 4-chloroquinolines. [From Baciocchi *et al.*,⁷ by permission of the American Chemical Society.]

Halogens. At all the positions investigated, these groups are rate-enhancing, i.e., the inductive effect predominates over the opposing resonance effect, a situation which is reflected in Hammett's σ_m - and σ_p -constants for side-chain reactions in the benzene series.^{60, 107} In agreement, the activating effect is in the order *epi* > *cata* and *pros* > *amphi*, because at the *cata* and *amphi* positions the opposing resonance

¹⁰⁷ D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

effect is stronger. The effects are transmitted quite strongly through the fused-ring system. The activating effect of a chloro group drops by a factor of only 1.7 on going from a *meta* to a *para* position (2-chloroquinoline) and by a factor of 3.5 on going from a *meta* to an *epi* position (4-chloroquinoline), i.e., there is an average fall-off factor of 1/2.6 between positions of the non-conjugative class in different rings.

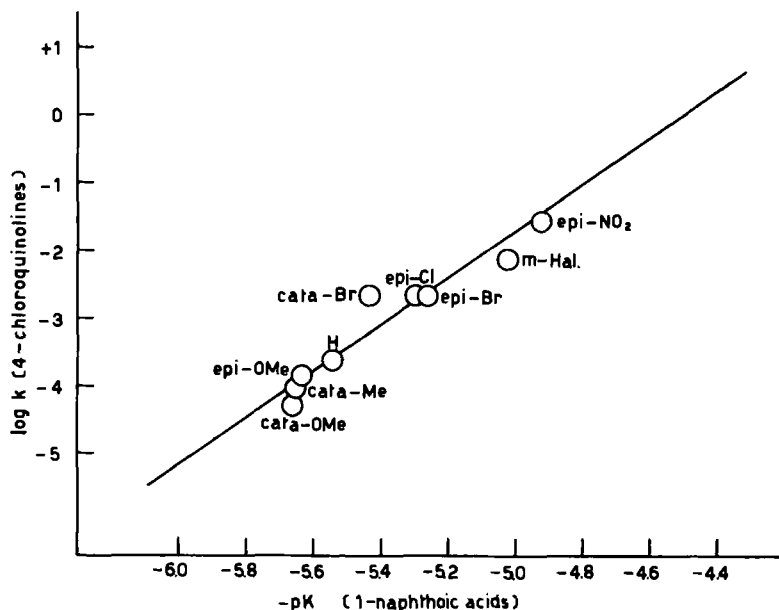


FIG. 5. Correlation of rate data ($\log k$) for the methoxy-dechlorination of substituted 4-chloroquinolines with the acid strengths ($\log K_a$) of 1-naphthoic acids.

VI-Group Substituents. Alkoxy groups are perhaps the most interesting substituents so far investigated in this reaction. Contrary to what might be expected from Hammett's σ_m -constants, which are positive for such groups, a consistent deactivating effect is observed for all the non-conjugative positions tested. In fused-ring systems, this increased relative importance of the conjugative over the inductive effect is attributed⁸⁷ to a combination of two factors acting in the same direction. One involves the change in aromatic character on going from the benzene ring to the fused-ring system, and the other

involves the direct interaction of the substituent with the aza group as illustrated by structure 47. Indications of the independent operation of both factors are available, since the effect has been observed with

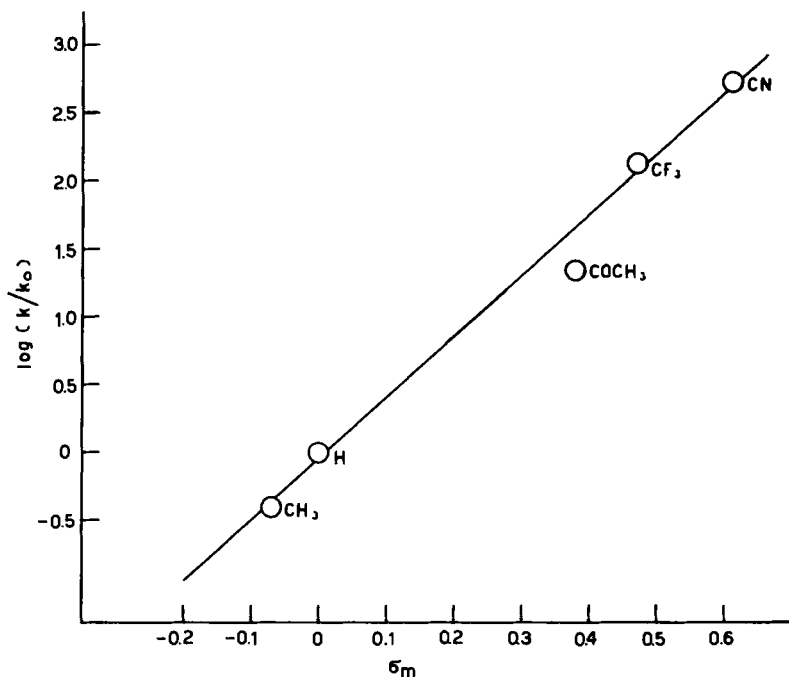
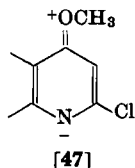


FIG. 6. The Hammett plot for the methoxy-dechlorination of *meta*-substituted 2-chloroquinolines.

naphthalene derivatives for other reactions¹⁰⁸ and with nitro-activated benzene derivatives for nucleophilic substitution.¹⁰⁹ More evidence is needed, however. If the above interpretation is correct, a

¹⁰⁸ C. C. Price and R. H. Michel, *J. Am. Chem. Soc.* **74**, 3652 (1952); K. C. Schreiber and R. G. Byers, *ibid.* **84**, 859 (1962).

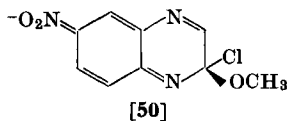
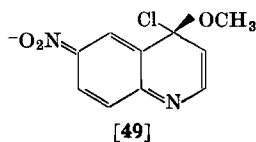
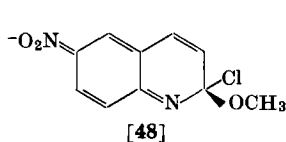
¹⁰⁹ M. Liveris, P. G. Lutz, and J. Miller, *J. Am. Chem. Soc.* **78**, 3375 (1956).

m -OCH₃ group should lower the basicity of naphthoic acids (both α and β) and the nucleophilic reactivity of aza-benzene derivatives. In terms of σ , the substituent effect for alkoxy groups will be negative at all positions. The m -SCH₃ group behaves similarly.

Amino Substituents. The only amino substituent investigated is a *cata*-N(CH₃)₂ group which, as expected, is strongly deactivating. At non-conjugative positions, the enhanced electron-releasing effects will be even more pronounced than those described for the alkoxy groups because of the stronger electron-releasing power of the amino nitrogen. Hammett's σ_m -constant for the amino group is negative and therefore no change in sign is expected in the present reaction.

Alkyl Groups. In the class of non-conjugative positions, the observed order of the deactivating effect of the methyl group is *meta* > *pros* (2-chloroquinoline), and the fall-off factor is 1/1.3 in this case. The fall-off factor is near unity if the effects from the *meta* position and the conjugative *cata* positions are compared (4-chloroquinoline), which indicates that the deactivating effect orders are *cata* > *epi* and *amphi* > *pros* as predicted by the "benzenoid" order *para* > *meta*.

Nitro and Other Electron-Withdrawing Substituents. The presence of unsaturated groups such as nitro at conjugative positions should cause strong resonance interaction in the transition state since a nucleophilic reagent is electron-repelling (structures 48-50). At positions of the



non-conjugative class no special enhancement of electron-withdrawing power should be obtained since no important direct interaction with either the reaction center or the aza group can occur. In accordance with this, the activating effects at the former positions are all substantially higher ($\sim 10^3$) than those at the latter ($\sim 10^2$). The still quite high activation of the non-conjugative positions (*epi* in 4-chloroquinoline and *pros* in 2-chloroquinoxaline) shows that with

this type of substituent the inductive effect is also strongly transmitted through the fused-ring system. The *meta*-nitro group in the quinoline series is difficult to study, since it undergoes displacement under nucleophilic attack more readily than halogen. A number of other *meta*-electron-withdrawing substituents, including CN, CF₃, COCH₃, and aza, were considered instead. Their use for a quantitative treatment of substituent effects is given in Section IV, C, 1, d.

b. *Piperidino-Dechlorination*. Some data on substituent effects are available for the reaction of piperidine with 4-chloroquinoline under pseudo-first-order conditions.¹¹⁰ These data involve the methyl group at *peri*, *cata*, and *ana* positions and the Cl group at *cata*, *epi* and *ana* positions (see Section VII). Here again, activation energies and log A values show mainly random variations, but the effects can be easily interpreted in terms of relative rates. Except for the *peri* position, linear structural correlations were found with basicity and with methoxy-dechlorination. In the latter case, it was surprising to find nearly identical selectivities for two reactions involving a change in both the nucleophilic atom and the charge type.

c. *Steric Effects*. The reactions of 5-substituted-4-chloroquinolines show fairly large primary steric effects. It is interesting to compare the effect of a nitro group at the non-conjugative positions 5 (*peri*) and 7 (*epi*).¹⁰⁵ As shown in Table IX the reaction in the former case is about 15 times slower than that in the latter case and the rate-depression is completely accounted for by the decrease in entropy of activation, indicating a reduced number of degrees of freedom¹¹¹ in the transition state of the more hindered structure (see Section VII). A similar rate effect is found in the reaction with piperidine where a *peri*-methyl group shows a deactivation factor of about 8 with respect to hydrogen, much too large for the operation of a polar effect alone.¹¹⁰ Secondary steric effects are discussed in Section IV, A, 2.

d. *Quantitative Treatments*. Figures 2-6 show a number of free-energy correlations which may be used for a quantitative assessment of heteroaromatic reactivity. The problem of obtaining a reliable set of substituent constants for use in nucleophilic aromatic substitution is still considered to be at an early stage, since the results of only a few *ad hoc* studies are available.¹¹² A study of heteroaromatic reactivity

¹¹⁰ R. H. Bailey, Ph.D. Thesis, University of North Carolina, Chapel Hill, N.C., 1958; *Dissertation Abstr.* **19**, 2460 (1959).

¹¹¹ See Ref. 106, pp. 410-412.

¹¹² See, for example, J. Miller, *Australian J. Chem.* **9**, 61 (1956).

should help because of the ready availability of structures in which *meta* substituents can occur without the intervention of steric effects. However, fused-ring systems of the homocyclic series have unfortunately been little investigated, even with the classic "side-chain" reactions. One possible extension of the original form of the Hammett equation [Eq. (10)] to naphthalene derivatives requires the determina-

$$\log(k/k_0) = \rho\sigma \quad (10)$$

tion of the dissociation constants of α - and β -naphthoic acids (structures 41 and 42) and of the substituent effects in both rings. Using the convention that in each of these reaction series the reaction constant is 1 in water at 25°C, the ΔpK_a values could be used as a basis for development of the extended Hammett equations (11) and (12) for use in the naphthalene series.

$$\log(k/k_0) = \rho_\alpha\sigma \quad (11)$$

$$\log(k/k_0) = \rho_\beta\sigma \quad (12)$$

Recently, Eq. (11) was extensively studied by Dewar and Grisdale,¹¹³ who synthesized several substituted 1-naphthoic acids and determined the dissociation constants in mixed aqueous solvents in connection with a study on the mechanisms of transmission of the inductive effect.¹¹⁴

Following the suggestion of Taft,¹¹⁵ substituent effects can be "stored" in σ -units by use of the Hammett equation for any category of reaction¹¹⁶ according to Eq. (13).

$$\bar{\sigma} = \frac{1}{\rho} \log(k/k_0) \quad (13)$$

At present, the most probable value of the reaction constant for the methoxy-dechlorination of 4-chloroquinolines is obtained from Eq.

¹¹³ M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.* **84**, 3546 (1962).

¹¹⁴ J. Hine, "Physical Organic Chemistry," p. 92. McGraw-Hill, New York, 1962.

¹¹⁵ R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.* **81**, 5343 (1959); R. W. Taft, Jr., *J. Phys. Chem.* **64**, 1805 (1960).

¹¹⁶ The method involves the following steps: (1) Select a number of (especially) *meta* substituents whose σ parameters can be considered invariant to use as a basis for the determination of the reaction constant ρ , (2) evaluate ρ , and (3) evaluate the $\bar{\sigma}$ parameters for the remaining substituents according to Eq. (13).

(11), which is plotted in the form of a $\log k$ vs. $\log K_a$ diagram in Fig. 5. The least squares value for the ρ_x constant obtained by this procedure is + 5.2: it will be obviously subject to change as more *meta* and *epi* substituents become available. Only the *cata*-NO₂ group was excluded from the above plot because it causes a strongly enhanced resonance effect in nucleophilic substitution (Section IV, C, 1, a) and an anomalous effect of uncertain origin in the dissociation of carboxylic acids.^{115, 117} It can be assumed that the reaction constant for 4-chlorocinnolines is essentially the same at the same temperature. Its essential identity with the selectivity of piperidino-dechlorination is mentioned in Section III.

For the 2-chloroquinoline series, the available data allow a different kind of approximation. It has been suggested⁸⁷ that benzenoid σ_m -constants for electron-withdrawing substituents may be a suitable select group of parameters for evaluation of S_N reaction constants. The plot thus obtained is shown in Fig. 6 and yields a line of slope + 4.5. This is considered to be a good approximation to the ρ_p -value for this series. From the plot all conjugatively electron-releasing groups were excluded except methyl, because of the enhanced conjugation effect ascertained for such groups (Section IV, C, 1, a). It can be assumed that the reaction constant for the 2-chloroquinoxaline series is essentially the same at the same temperature.

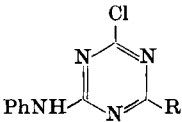
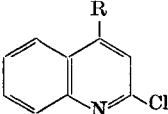
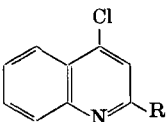
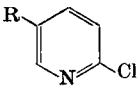
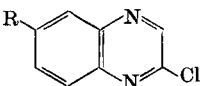
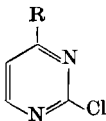
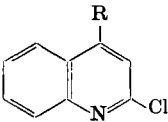
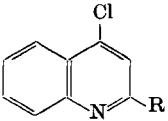
One of the merits of the above treatment, which justifies its inclusion in this review, is that it allows a quantitative comparison of the selectivity of nucleophilic heteroaromatic substitution (expressed by the reaction constant) with that for the analogous reaction with nitro-activated systems.^{4, 112} Values for the latter are in the range 3.5 to 5.0. The fact that in both cases high ρ -values of similar magnitude are found is consistent with the hypothesis of similar mechanisms for both classes of compounds.

Sets of homo- and hetero-nuclear substituent "constants" for the alkoxy-dechlorination of 4-chloroquinolines have been recently obtained from preliminary values of the ρ -constants^{7, 87} and can be extended and improved on the basis of the more extensive data now available. A detailed discussion on substituent constants would extend beyond the scope of this review. In general, it can be stated that unless enhanced resonance interaction occurs with the reaction center in the transition state (i.e., *para*-, *cata*-, *amphi*-NO₂ groups) or with the aza

¹¹⁷ E. Berliner and E. H. Winicov, *J. Am. Chem. Soc.* **81**, 1630 (1959).

TABLE XII

SOME COMPARISONS OF SUBSTITUENT EFFECTS IN THE NUCLEOPHILO-DECHLORINATION OF AZA-BENZENE AND AZA-NAPHTHALENE DERIVATIVES

Heteroaromatic compound	Nucleophile and conditions	Relative rate	Reference
<i>Chloro vs. alkoxy groups</i>		$k_{\text{Cl}}/k_{\text{OAlk}}$	
 <chem>Clc1nc(Nc2ccccc2)nnc1R</chem>	PhCH ₂ NH ₂ in THF, 40°	149 (OCH ₃) 163 (OC ₂ H ₅)	49
 <chem>Clc1c(R)nc2ccccc2n1</chem>	MeO ⁻ in MeOH, 75.2°	81 (OCH ₃) 82 (OC ₂ H ₅)	87
 <chem>Clc1c(R)nc2ccccc2n1</chem>	MeO ⁻ in MeOH, 75.2°	522 (OCH ₃) 470 (OC ₂ H ₅)	87
<i>Nitro group vs. hydrogen</i>		$k_{\text{NO}_2}/k_{\text{H}}$	
 <chem>Clc1cc(R)ncn1</chem>	piperidine in EtOH, 20°	7.3×10^6	20, 42
 <chem>Clc1c(R)nc2ccccc2n1</chem>	MeO ⁻ in MeOH, 5°	2.8×10^4	104
<i>Methyl group vs. hydrogen</i>		$k_{\text{CH}_3}/k_{\text{H}}$	
 <chem>Clc1cc(R)ncn1</chem>	piperidine in EtOH, 30°	1/2.4	42
 <chem>Clc1c(R)nc2ccccc2n1</chem>	MeO ⁻ in MeOH, 75.2°	1/2.5	87
 <chem>Clc1c(R)nc2ccccc2n1</chem>	MeO ⁻ in MeOH, 75.2°	1/3.2	87

group in the ground state (i.e., *meta*-, *epi*-, and *pros*-OR groups) the $\bar{\sigma}$ -parameters agree reasonably well with the available "constants" from naphthalene reactivities.¹¹⁸ It should be mentioned that the σ_m -(aza)-constants can be calculated by the above treatment. Values of +0.59 and +0.75 are obtained for the *alpha* and *beta* series, respectively. These values are for nuclear aromatic substitution: however, they are of comparable magnitude to those found for side-chain reactions,^{60, 119} ranging from +0.53 to +0.64.

2. Substituent Effects in the Aza-Benzene Ring

Reactions involving monocyclic six-membered heteroaromatic rings have not been studied sufficiently extensively to allow a quantitative treatment of substituent effects. However, comparison with aza-naphthalene reactivities indicates that aza- and polyaza-benzene systems must also be highly selective.

Table XII illustrates this point for a number of examples. The rate effect of a chloro group *relative to an alkoxy group*, as found with chloro-*s*-triazine derivatives, is intermediate between those found with 2- and 4-chloroquinoline derivatives. This is striking in that the substrate, the reagent type, and the solvent are different in the two reactions. This "constancy" in selectivity is noted in another instance in Section IV, C, 1, b. The rate effect of a *p*-nitro group on the reaction of 2-chloropyridine with piperidine is very large and shows, again, the high sensitivity of these reactions to structural changes. Assuming that the reaction constants for the different nucleophiles are of the same order of magnitude, comparison with an *amphi*-NO₂ group effect, which is also large, gives the expected order of reactivity, *para*-NO₂ > *amphi*-NO₂, both positions belonging to the conjugative class. Finally, in the chloropyrimidine series, the effect of a *m*-methyl group is very similar to that observed for chloroquinolines.

Chapman and his associates^{42, 47, 94} provide further examples of the rate effects of nitro and alkyl groups, some of which are mentioned in Section IV, A, 2. Additional data on *m*-alkyl groups are assembled in Table XIII. The effect of a *m*-methyl group in 2-chloropyrimidine, with a pathway through a ring-nitrogen atom is to lower the reactivity by a factor of 2.4; introduction of a second *m*-methyl causes an almost identical effect (2.5). For 4-chloropyrimidine it is shown

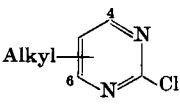
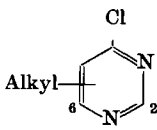
¹¹⁸ P. R. Wells and E. R. Ward, *Chem. Ind. (London)* 528 (1958).

¹¹⁹ G. Favini, *Rend. Ist. Lombardo Sci. Pt. I.* **91**, 162 (1957); G. Favini and S. Carrà, *Gazz. Chim. Ital.* **87**, 1367 (1957).

that the pathway through a ring-nitrogen atom relays the inductive effect of a *m*-methyl somewhat less efficiently than that through an all-carbon chain, and the ratio $k_{2-\text{Me}}/k_{6-\text{Me}}$ is 1.4. The reactivity of the unsubstituted 4-chloropyrimidine has not been determined because of the low stability of this substance. An estimate of the reactivity can however be obtained from the knowledge of the previously mentioned methyl-group effects in the 2-chloropyrimidine series on the assumption of essentially similar reaction constants in the two series. Thus, by multiplying the rate for 4-chloro-2-methylpyrimidine by 2.4, a k value of 7.2×10^{-3} (liter mole⁻¹ sec⁻¹) at 30° results. This is a somewhat different estimate from that obtained previously from the activation parameters, 1.4×10^{-3} at 20°,⁹⁴ allowance being made for the temperature effect.

TABLE XIII

THE EFFECT OF ALKYL SUBSTITUENTS ON THE REACTIVITY OF CHLOROPYRIMIDINE^a

						
	H	4-CH ₃	4,6-(CH ₃) ₂	2-CH ₃	6-CH ₃	6-C(CH ₃) ₃
10 ⁴ <i>k</i> (30°)	6.70	2.80	1.13	30.0	21.4	8.33

^a Piperidino-dechlorination in ethanol (k given in liter \times mole⁻¹ \times sec⁻¹). Data from refs. 42 and 94.

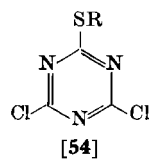
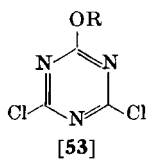
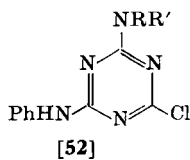
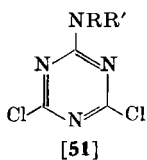
The greater electron-releasing capacity of a *m*-C(CH₃)₃ group than a *m*-CH₃ group ("inductive order") is seen from the above data. The reactivity of the *t*-butyl derivative is of value in studies concerned with the steric effect of the NO₂-activated analogues of *N*-heterocyclic compounds (Section IV, A, 2).

As to the electron-withdrawing substituents, the activating effect of a nitro group in the piperidino-dechlorination of 2-chloropyridine involves factors of 7.3×10^6 and 4.5×10^6 from the *para* and *ortho* positions, respectively.^{20, 42} An *ortho*-cyano group was found to be

markedly less activating than an *ortho*-nitro group, but still strongly activating with respect to hydrogen. Thus, the reaction of 2-chloro-3-cyano-5-nitropyridine with aniline at 20° was estimated to be about 7×10^3 times as fast as that of 2-chloro-5-nitropyridine.⁴⁷ As expected, this activation is much greater than that of a *meta*-cyano group, which is of the order of 10^2 (Section IV, C, 1, a).

The high reactivity of trichloro-*s*-triazine and tetrachloropyrimidine, the ease of replacement of the first chlorine atom from these compounds with several types of nucleophiles (amines, alcohols, etc.) and, finally, the important role of these reactions in dye chemistry have stimulated many investigations dealing with substituents of the general types RZ and R₂Z, where Z is an electron-donor atom or group (NH, O, S, N).

Data by Matsui *et al.*²⁷ and Goi^{49, 50} for the reactions of chloro-*s*-triazine derivatives of series **51** and **52** are assembled in Table XIV.



The influence on the rate of the diverse alkylamino groups relative to NH₂ appears to vary over a rather narrow range and involves deactivating factors of 1.4 or less. It is noteworthy that both *N*-morpholino and phenylamino groups are activating and involve maximum factors of 3.1 and 12, respectively.

Substituents in chloro-*s*-triazine derivatives can only occupy positions *meta* to the displaced group and *ortho-para* to the aza groups. The situation is thus similar to that encountered in 2,4-disubstituted quinolines (Section IV, C, 1, a). Unshared *p*-electrons from the side-chain nitrogen or oxygen atom are expected to interact conjugatively with an *aza* group, as shown by structure **55**, and to give rise to special substituent effects that cannot be predicted by normal Hammett σ_m -constants. Goi's application⁴⁹ of the Hammett equation with the use of these constants is therefore believed to be misleading with regard to the evaluation of reaction constants for series of compounds of types **51** and **52**. The contribution of structures such as **55** is rate-depressing. It is well known from preparative chemistry that successive substitution of the chlorine atoms in polychloroazines by amino

TABLE XIV

EFFECT OF SOME NITROGEN-, OXYGEN-, AND SULFUR-CONTAINING GROUPS ON THE RATE CONSTANTS FOR THE REACTION OF CHLORO-*s*-TRIAZINE DERIVATIVES WITH VARIOUS NUCLEOPHILES

Substituent	Aniline in acetone, at 35° ^a	<i>p</i> -Toluidine in THF, at 40° ^b	Benzylamine in THF, at 40° ^c	Water in aqueous acetone, at 40° ^d (Z = O)	Water in aqueous acetone, at 40° ^d (Z = S)
NH ₂	0.0142	0.202	0.652		
NHCH ₃	0.0125	0.175	0.463		
NHC ₂ H ₅	0.0110	—	0.495		
NHC ₄ H ₉ (<i>n</i>)	0.0109	—	0.465		
N(CH ₃) ₂	—	0.195	0.544		
<i>N</i> -morpholino	—	0.620	1.56		
NHC ₆ H ₅	—	2.40	3.24		
N(CH ₃)C ₆ H ₅	—	0.951	—		
<i>n</i> -C ₄ H ₉ Z				0.09	0.12
C ₆ H ₅ Z				0.58	0.30

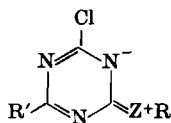
^a Series: 2-amino-4,6-dichloro-*s*-triazine; *k* in liter × mole⁻¹ × min⁻¹. Ref. 27.

^b Series: 2-amino-4,6-dichloro-*s*-triazine; *k* in liter × mole⁻¹ × sec⁻¹. Ref. 50.

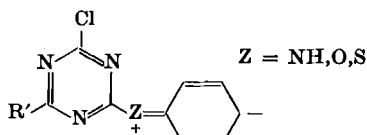
^c Series: 2-amino-4-anilino-6-chloro-*s*-triazine; *k* in liter × mole⁻¹ × sec⁻¹. Ref. 49.

^d Series: 2-substituted-4,6-dichloro-*s*-triazine; *k* in hr⁻¹. Ref. 39.

or alkoxy groups markedly slows down further reaction, allowing isolation of the intermediate products, with obvious preparative value. Goi found that in the reaction with benzylamine the deactivating effect of a dimethylamino group *with respect to a chlorine atom* involves a factor of 17,000 and that of a methoxy group a factor of 150 (see below).



[55]



[56]

The effects of some oxygen- and sulfur-containing groups on the rate of hydrolysis of chloro-*s*-triazine derivatives (53 and 54) have been recently reported.³⁹ Many of the substituents considered belong to the general type $O(CH_2)_nX$ or $S(CH_2)_nX$ and have only a small effect on the rates *with respect to the* $OBu(n)$ *or* $SBu(n)$ *group*. With a phenoxy or phenylthio group a considerable rate increase is obtained. This effect is shown in Table XIV and is substantially similar to that noted above for the phenylamino group. The rate enhancement can be attributed to competitive conjugative interaction of the phenyl group resulting in a diminished electron supply to the heterocyclic ring, as illustrated by structure 56.

Any discussion on the data reported in Table XIV suffers from two relevant shortcomings, the lack of a comparison of the substituent effects *with respect to the effect of the hydrogen atom* and the lack of information on substituents of widely different types. For example, it would be of interest to know the exact position of the hydrogen atom in Goi's reactivity sequences



and



Because of the similarity of the substituent effects in *s*-triazine and quinoline derivatives, it seems probable that in the former sequence hydrogen falls between the chlorine atom and the methoxy group.

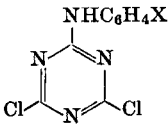
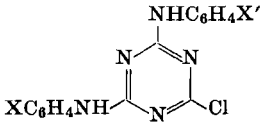
3. Normal and Anomalous Behavior of Arylamino Substituents

Matsui *et al.*²⁷ and Goi^{28, 50} have extensively studied substituent effects in the aromatic ring of anilino groups attached to nuclear

positions of a chloro-*s*-triazine system. The relative reaction rates are shown in Table XV. There is no direct conjugative interaction between the substituent X and the *aza* groups which are *ortho* or *para* to the anilino group. Electron-releasing substituents should not display

TABLE XV

RELATIVE RATES OF AMINO-DECHLORINATION OF SUBSTITUTED
ANILINO-*s*-TRIAZINE DERIVATIVES

					
X	Aniline in acetone, ^a 35°	<i>p</i> -Toluidine in THF, ^b 40°	X	X'	Benzylamine in THF, ^c 40°
H	1	1	H	H	1
<i>o</i> -CH ₃	0.535	—	H	<i>m</i> -CH ₃	0.865
<i>m</i> -CH ₃	0.922	0.921	H	<i>p</i> -CH ₃	0.778
<i>p</i> -CH ₃	0.685	0.708	H	<i>p</i> -OCH ₃	0.624
<i>o</i> -OCH ₃	1.41	—	H	<i>p</i> -Cl	1.78
<i>m</i> -OCH ₃	1.22	—	H	<i>m</i> -NO ₂	4.35
<i>p</i> -OCH ₃	0.492	0.566	<i>m</i> -CH ₃	<i>m</i> -CH ₃	0.664
<i>p</i> -OC ₂ H ₅	0.491	—	<i>p</i> -CH ₃	<i>p</i> -CH ₃	0.553
<i>o</i> -Cl	2.76	—	<i>p</i> -CH ₃	<i>p</i> -Cl	1.32
<i>m</i> -Cl	2.99	—	<i>p</i> -OCH ₃	<i>p</i> -OCH ₃	0.370
<i>p</i> -Cl	1.96	2.13	<i>p</i> -Cl	<i>p</i> -Cl	3.12
			<i>p</i> -Cl	<i>m</i> -NO ₂	8.03
			<i>m</i> -NO ₂	<i>m</i> -NO ₂	18.6

^a Ref. 27.

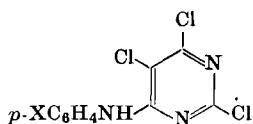
^b Ref. 50.

^c Ref. 28.

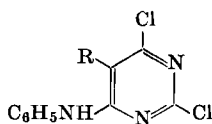
especially exalted resonance effects. In agreement, a *m*-methoxy group, unlike its behavior as a "direct" substituent in the hetero-aromatic ring, is "normally" activating. Use of Hammett's σ -constants from benzenoid reactivities appears to be suitable for a quantitative correlation of these data. The linear plots obtained from the

equations $\log(k/k_0) = \rho\sigma$ or $\log(k/k_0) = \rho\Sigma\sigma$ are significant in that they involve different types of substituents including chloro and alkoxy as well as alkyl and nitro groups. Despite the high sensitivity of the reaction to substituent effects, the relative rates are not widely spaced and, therefore, reaction constant values are as low as *ca.* 1. This is the obvious consequence of the fact that the polar effects of the substituent X are relayed to the reaction center across the arylamino fragment. In the hydrolysis of some *p*-substituted 2-aryl-4,6-dichloro-*s*-triazines in aqueous acetone,³⁹ a slightly higher reaction constant, +1.3, was obtained, in accord with the absence of the amino-nitrogen bridge in the above-mentioned fragment.

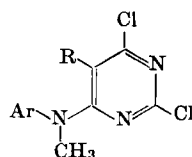
Ackermann and Dussy²³ have recently described some interesting anomalous effects of substituents on reaction rates. In structure **57**,



[57]



[58]



[59]

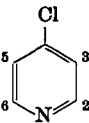
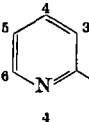

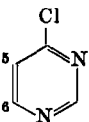
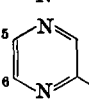
electron-attracting substituents in the arylamino side-chain ($X = \text{Cl}$, SO_2CH_3 , NO_2) have a definite deactivating influence on the alkoxy-dechlorination reaction. Similarly, the effect of replacement of hydrogen by chlorine in structure **58** is one of slight deactivation. Similar structural changes produce normal kinetic effects in the *N*-methyl derivatives (structure **59**). The anomaly has been shown to be caused by the conversion of the weakly acidic structures **57** and **58** into the corresponding conjugate bases by the alkoxide ion (Section II, B). Enhanced conjugation in these bases results in rate-depression.

4. Annellation Effects

It is of interest to compare the reactivity of aza-benzene derivatives to that of related fused-ring systems. The structural change involved may be formally treated as the insertion of the bidentate substituent $(\text{CH})_4$ and has been frequently called "annellation." Essentially, it involves a change in the aromaticity of the ring system which can be traced back to fundamental theoretical parameters (bond-orders). Generally annellation is accompanied by a fairly large increase in reactivity which can be attributed to the expanded region available for delocalization of the charge in the transition state. Several examples

of annelation effects in two typical reactions are collected in Table XVI. The marked deactivating effect observed for the 4,5-annelation of 2-chloropyridine (3-chloroisoquinoline) has been ascribed by Chapman²⁰ to bond fixation.

TABLE XVI
ANNELATION EFFECTS^a

Parent substrate	Derivative (annelation)	C ₂ H ₅ O ⁻ , (° C)		Piperidine, (° C)
	4-Chloroquinoline (2,3)	7.5	(20)	3.7 (125)
	9-Chloroacridine (2,3 and 5,6)	710	(20)	—
	1-Chloroisoquinoline (3,4)	310	(20)	37 (75.2)
	3-Chloroisoquinoline (4,5)	5.5 × 10 ⁻³	(20)	—
	2-Chloroquinoline (5,6)	290	(20)	73 (75.2)
	2-Chloroquinazoline (5,6)	1.4	(20)	—
	4-Chloroquinazoline (5,6)	—		~ 1000 (30)
	2-Chloroquinoxaline (5,6)	—		13 (75.2) ^b

^a Rates relative to the parent substrate. Data from refs. 20 and 43. Reactions in ethanol unless otherwise stated.

^b Reactions in toluene.

D. REACTIVITY OF HETEROCYCLES CONTAINING OTHER THAN SIX-MEMBERED RINGS

The reactivity of halogeno-substituted five-membered ring heterocycles with regard to nucleophilic attack is somewhat greater than that

TABLE XVII
RELATIVE REACTIVITIES OF FIVE- AND SIX-MEMBERED RING HETEROCYCLES

Five-membered ring compound (I)	Six-membered ring compound (II)	k_I/k_{II}	Reference
<i>Reactions with piperidine at 75.2°</i>			
2-Chlorothiazole	2-Chloropyridine	35	43
2-Chlorobenzothiazole ^a	2-Chloroquinoline ^a	46	43, 98
2-Bromo-5-nitrothiophene ^b	4-Bromo-1-nitrobenzene ^b	150	121
<i>Reactions with alkoxide ion at 25°</i>			
2-Chlorobenzothiazole (CH_3O^-)	2-Chloroquinoline ($\text{C}_2\text{H}_5\text{O}^-$)	450	122

^a Reaction in toluene.

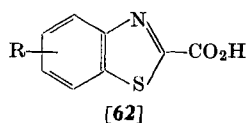
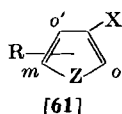
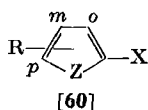
^b Determined at 25°.

of the corresponding halogenobenzenes. Thus, chloro- and bromofuran react about ten times as fast as chloro- and bromobenzene, respectively.¹²⁰

Conditions more accessible to rate measurements and, possibly, more favorable to a "normal" course of substitution (Section II, A) make the use of activated compounds such as nitro- and aza-substituted derivatives desirable. In both cases, the activated halogeno-substituted five-membered ring heterocycle is also more reactive than a similarly activated six-membered ring compound.^{43, 98, 121, 122} This point is shown in Table XVII.

Some additional structural relations can be deduced from the data of Amstutz *et al.*^{43, 123} In the reactivity of 2-chlorobenzothiazole with piperidine a 50-fold rate-enhancing annelation effect seems to occur (rate relative to 2-chlorothiazole; a solvent effect is neglected). Aza-activation is of the order of 10^6 (rate relative to 2-bromothianaphthene; a leaving-group effect is neglected). In both of these cases, the observed behavior roughly parallels the corresponding properties of six-membered ring heteroaromatics.

Studies on substituent effects are scanty. For the five-membered monocyclic nuclei, the relative positions have been compared to the classic *ortho*, *meta*, and *para* positions of benzene derivatives according to formulae **60** and **61**. This comparison is based on the assumption



that group Z behaves as an insulating bridge in the molecule. The reactivities of the six isomeric bromo-nitrothiophenes¹²¹ show some characteristics similar to those of the bromo-nitrobenzenes, e.g. the high *o*:*p* ratios in the reaction with piperidine. On the other hand, the analogy is hardly more than qualitative; also, it suffers from a significant exception: 2-bromo-4-nitrothiophene (a "*meta*" derivative) reacts much faster than either 2-bromo-3-nitro- ("*ortho*") or 2-bromo-5-nitro-thiophene ("*para*"). This effect is not easily explained and has

¹²⁰ D. G. Manly and E. D. Amstutz, *J. Org. Chem.* **22**, 133 (1957).

¹²¹ R. Motoyama, S. Nishimura, Y. Murakami, K. Hari, and E. Imoto, *Nippon Kagaku Zasshi* **78**, 950 (1957).

¹²² P. E. Todesco and P. Vivarelli, *Gazz. Chim. Ital.* **92**, 1221 (1962).

¹²³ K. R. Brower and E. D. Amstutz, *J. Org. Chem.* **19**, 411 (1954).

no counterpart in spectral behavior but indicates that the positions occupied by R in formulae **60** and **61** are not true *ortho*, *meta*, and *para* positions.

A few substituent effects on the reactivity of 5-R-2-halogenofurans ($R = \text{CH}_3$, $\text{CONC}_5\text{H}_{10}$, CO_2CH_3 ; see Section VII) have also been reported.¹²⁰ In this series the methyl group causes a 2.2-fold decrease in the rate.

The kinetic effects of some substituents on the fused benzene ring (CH_3 , NO_2 , OCH_3 , Cl) have been determined recently¹²² for the reaction between the methoxide ion and the series of compounds α -R-2-chlorobenzothiazole. Some of these effects are compared in Table XVIII with those observed at the 6-position of 2-chloroquinolines and quinoxalines which are of the conjugative class. The data for

TABLE XVIII
SUBSTITUENT EFFECTS FOR THE METHOXY-DECHLORINATION OF
SOME FUSED-RING SYSTEMS^a

Substrate	T, °C	6-Cl	6-NO ₂	Reference
2-Chlorobenzothiazole	25	5.9	510	122
2-Chloroquinoline	75.2	6.2	800	104
2-Chloroquinoxaline	5	5.8	2000	104

^a Rates relative to the corresponding parent chloroheterocycle.

the 6-chloro substituent indicate that there is a remarkable similarity in the selectivity of the above systems with regard to attack by the same reagent. In the benzothiazole ring, however, a 6-nitro group shows somewhat less ability to accept the electronic charge in the transition state, a fact which is probably related to the smaller efficiency of the sulfur bridge in the transmission of polar influences.

Indications of the relative efficiencies of transmission through either aza or sulfur in benzo derivatives can be obtained from Jaffé's empirical multiple regression approach.¹²⁴ In these systems, just as in aza-naphthalenes (Section IV, C, 1, d), knowledge of the dissociation

¹²⁴ H. H. Jaffé, *J. Am. Chem. Soc.* **76**, 4261 (1954); M. S. Melzer, *J. Org. Chem.* **27**, 496 (1962).

constants of the heteronuclearly substituted carboxylic acids (62) is desirable for a proper extension of the Hammett equation.

E. THE LEAVING-GROUP EFFECT

The relative mobilities of groups undergoing displacement has been much studied in nitro-activated systems but has received little attention in heteroaromatic substitution reactions. From a survey of the available studies, a number of relative mobilities can be deduced for Cl, Br, and I in some aza-activated compounds,^{8, 98} *N*-oxides,^{32, 125} and five-membered ring compounds.^{33, 120} These data are reported in Table XIX. Despite the large variety of substrates, the three halogens are usually displaced at rates varying well within one order of magnitude. The most frequent order observed with pyridine and quinoline derivatives and their *N*-oxides is $\text{Br} > \text{Cl} > \text{I}$, whereas with 2-halogenonitrothiophenes the order $\text{Cl} > \text{Br} > \text{I}$ was obtained.

The usual order found with halogenonitrobenzenes is $\text{F} \gg \text{Cl} \sim \text{Br} \sim \text{I}$, the order of Cl and Br being variable, just as in heteroaromatic reactivity. The position of fluorine is of interest: the available data indicate that it is usually the same as for nitrobenzene derivatives. Thus, in acid hydrolysis the order $\text{F} \gg \text{Cl}$ for 2-halogenoquinolines⁴⁶ can be deduced beyond doubt since the fluoro derivative appears to react in the non-protonated form and the chloro derivative to resist hydrolytic attack even in the protonated form under appropriate conditions (Section II, D, 1, d). Furthermore, in the benzo-thiazole ring, fluorine is displaced by the CH_3O^- reagent at a rate 10^3 times that for chlorine.⁸¹

The order $\text{NO}_2 \gg \text{Cl}$, which is known for the reactions of nitro-activated aromatic compounds, is also found for pyridine and quinoline derivatives. In the reaction of 2-chloro-4-nitroquinoline with methoxide ion, only the 4-methoxide derivative is formed, as shown by gas-chromatography, whereas 2,4-dichloroquinoline yields a mixture of the isomeric chloro-methoxy derivatives in comparable amounts.^{99, 126}

In 2-substituted dinitrothiophenes, phenylsulfone and *p*-nitrophenoxy groups both react faster than the chloro group with pyridine, i.e., in a reverse order with respect to 1-substituted-2,4-dinitrobenzenes,³³ although with both substrates the factors involved are small.

¹²⁵ Z. Talik, *Bull. Acad. Polon. Sci., Ser. Sci.* **9**, 561 (1961).

¹²⁶ S. Fatutta and G. Illuminati, unpublished work.

TABLE XIX
RELATIVE MOBILITIES OF HALOGEN ATOM SUBSTITUENTS^a

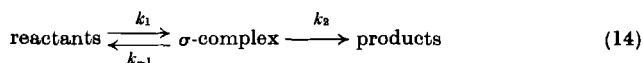
Substrate	Conditions	Cl	Br	I	Reference
<i>N-Heteroaromatic compounds</i>					
2-Halogenopyridine	Piperidine, 75.2°	1	9.3	—	43, 98
2-Halogenoquinoline	Piperidine, 75.2°	1	3.4	—	98
4-Halogenoquinoline	Piperidine in 70% EtOH, 130°	1	1.3	0.6	32
4-Halogenoquinoline	Piperidine in 96% EtOH, 130°	1	2	1.2	32
2-Halogeno-5-nitropyridine	Acid hydrolysis, 25°	1	—	0.23	8
<i>N-Oxides</i>					
2-Halogeno-4-methoxypyridine <i>N</i> -oxide	CH ₃ O ⁻ , reflux temp.	1	~ 1	~ 0.3	125
2-Halogeno-4-nitropyridine- <i>N</i> -oxide	Et ₂ NH in alcohol, reflux temp.	1	~ 2	~ 0.3	125
4-Halogenoquinoline <i>N</i> -oxide	Piperidine in 70% EtOH, 80°	1	1.3	0.33	32
4-Halogenoquinoline <i>N</i> -oxide	Piperidine in 95% EtOH, 90°	1	1.4	0.40	32
<i>Five-membered rings</i>					
2-Halogenofuran	Piperidine, 200°	1	8.7	18	120
2-Halogeno-3-nitrothiophene	Piperidine in EtOH, 25°	1	0.55	0.064	33
2-Halogeno-5-nitrothiophene	Piperidine in EtOH, 25°	1	0.64	0.076	33
2-Halogeno-3,5-dinitrothiophene	Piperidine in EtOH, 25°	1	0.48	0.38	33

^a Reaction rates relative to the chloro derivative.

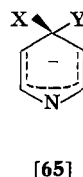
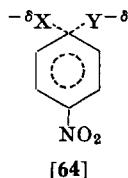
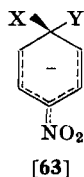
The above examples indicate a general behavior which roughly parallels that found in homocyclic aromatic systems. The less usual order, $I > Br > Cl$, found for the non-activated halogenofurans is reminiscent of the similar order $I > Br > Cl > F$, observed by Tronov and Krüger for the halogenobenzenes.¹²⁷ Again, it would be of interest to establish the position of fluorine in the order of reactivity of the halogenofurans.

V. A General Comment on Mechanism

The preceding Sections illustrate several experimental features of heteroaromatic substitutions. It is now intended to comment on some of these features which are most significant in terms of reaction mechanism. As stated in the Introduction, a possible mechanism of nucleophilic bimolecular aromatic substitution reactions is that represented by Eq. (14), where an intermediate of some stability



(σ -complex), corresponding to structure **63**, is formed.^{2, 5} An alternative mechanism is represented by Eq. (15).



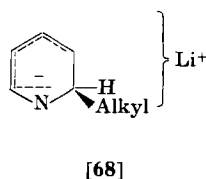
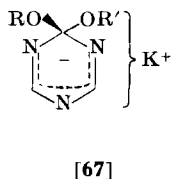
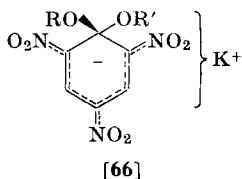
The latter mechanism is characterized by a transition-state structure of type **64** and by its being (in part) analogous to the S_N2 mechanism at a saturated carbon. The preference of a two-step mechanism to the apparently simpler one-step mechanism is suggested by the isolation of Meisenheimer complexes¹²⁸ and by the kinetics of their formation.¹²⁹ The experimental evidence on these

¹²⁷ B. Tronov and E. Krüger, *J. Russ. Phys.-Chem. Soc.* **58**, 1270 (1926); *Chem. Zentr.* II, 1145 (1927); *Chem. Abstr.* **12**, 3887 (1927).

¹²⁸ J. Meisenheimer, *Ann. Chem.* **323**, 205 (1902).

¹²⁹ J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.* 2528 (1956).

compounds has recently been reviewed in detail.^{4, 5} Although such evidence is confined to the most highly nitro-activated compounds (**66**), it seems legitimate to suspect a general tendency of activated structures to form σ -complexes of some stability. Meisenheimer-type complexes such as **67** have never been reported in heteroaromatic



chemistry, but adducts of a similar kind (**68**) have been isolated¹³⁰ using special nucleophilic reagents (alkyllithium).

The difference between the mechanisms represented by Eqs. (14) and (15) is actually (but not conceptually) immaterial as long as the transition state of the rate-determining step (RDTS) has a structure closely resembling that of the σ -complex. The difference is that shown in the potential-energy diagram of Fig. 7 (A) and is kinetically undetectable. What is then most fundamental is to consider the structure of RDTS. Experimental evidence points overwhelmingly to the great importance of bond-making as implied by structures **63** or **65**. The main evidence can be summarized as follows.

(i) *Tendency to σ -complex formation.* This property, which has just been mentioned, shows that it is *possible* (and not merely hypothetical) for the C—X bond to remain essentially intact while the C—Y bond is fully formed, with the hybridization change $sp^2 \rightarrow sp^3$ of the aromatic carbon atom. This is a major structural difference with respect to substitution at a saturated carbon atom.

(ii) *Leaving-group effects.* The order of mobilities of halogens in both S_N1 and S_N2 mechanisms, i.e., $I > Br > Cl > F$, is that predicted from the relative strengths of the C—halogen bonds.¹³¹ Usually this order is found to be profoundly altered in nucleophilic aromatic substitution reactions and also with heteroaromatic systems (Section IV, E). The predominant importance of the electronegativity of the group when it is still an integral part of the substrate is shown by the order $F \gg Cl$ and

¹³⁰ K. Ziegler and H. Zeiser, *Ber.* **63**, 1847 (1930).

¹³¹ A. Streitwieser, Jr., "Solvolytic Displacement Reactions." McGraw-Hill, New York, 1962.

by the fact that several groups, such as Cl, Br, I, PhSO, PhSO₂, and *p*-O₂N—C₆H₄—O show approximately the same mobility.^{5, 132}

(iii) *Reaction selectivity (substituent effects)*. This property can be used as a diagnostic criterion of mechanism since a bimolecular attack is expected to be sensitive to the structure of the substrate to an extent depending on the role of the bond-making step. The importance of the

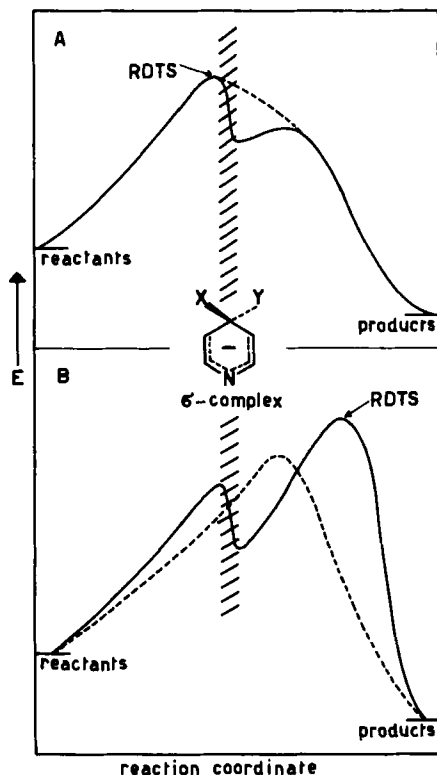
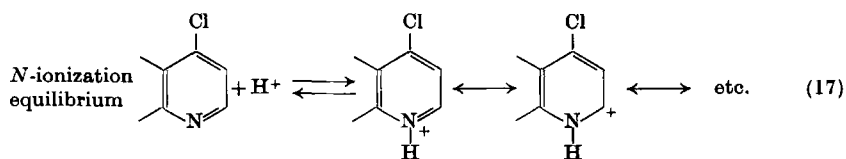
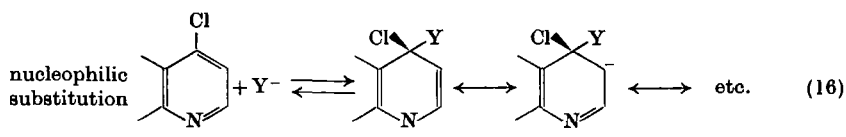


FIG. 7. Potential-energy diagrams for nucleophilic heteroaromatic substitutions. A, solid line: very probable and common; B, solid line: probable but less frequent; A and B, dotted lines: scarcely probable and/or infrequent.

latter in these reactions is shown by the following considerations. First, both nitro- and aza-activated systems show high reaction constants which are in the general range from +4 to +5 (Section

¹³² J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Am. Chem. Soc.* **79**, 385 (1957).

IV, C, 1, d). Second, for both classes of aromatic compounds such values show a surprisingly small dependence on the nature of the attacking reagent, probably indicating the predominant role of the reorganization of the substrate toward a new state represented by structure **63** or **65**. Finally, it may not be fortuitous that a correspondence is found between structural effects on substitution rates and on ionization constants (Section IV, C, 1, a). Bond-making would in fact be the essential analogy between these phenomena [Eqs. (16) and (17)], and



the correspondingly similar reorganizations would result in similar free-energies (or free-energies of activation).¹³³ Again, in Eq. (16), the final state of the equilibrium need not be an intermediate of some stability provided that the structure of the transition state approaches closely to it. It is of interest to recall that reactions (16) and (17) have similar reaction constants.

(iv) *Reaction selectivity (reagent effects)*. The sensitivity of the reactivity of the substrate to the nucleophilic power of the reagent clearly appears for systematic structural changes in the aniline reagent. The resulting fairly high value of the reaction constant (-3.4) is indicative of the importance of bond-making (Section III, A) with the attacked aromatic carbon.

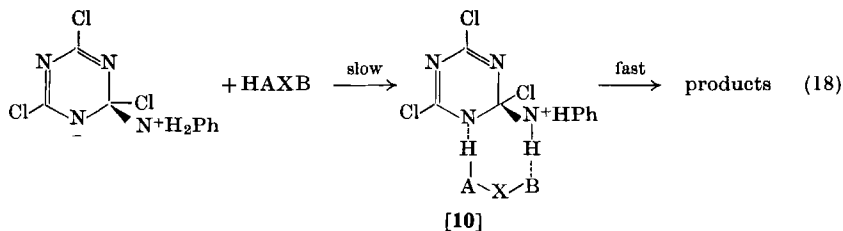
(v) *Volume changes of activation*. Despite some uncertainties in the interpretation of these rather uncommon data, a high degree of bond-making with diverse reagent types was indicated²⁴ with both halogenonaphthalenes and halogenoquinolines.

The above evidence shows that a high degree of bond-making in the rate-determining step of bimolecular nucleophilic substitutions seems

¹³³ G. S. Hammond, *J. Am. Chem. Soc.* **77**, 334 (1955).

to be a general property for various kinds of nitro- and aza-activated substrates. It is possible that in some special cases where bond-making *is not* rate-determining it may still be, however, the primary step of the reaction. For example, 1-halogeno-2,4-dinitrobenzenes are typical, highly reactive substrates to which the above generalizations concerning bond-making are applicable. Yet, under special conditions, bond-breaking is involved in the rate-determining step and the mobility order $\text{Cl} > \text{F}$ is found.^{134, 135} One such condition is the use of a dipolar aprotic solvent where drastically reduced assistance to solvation of the leaving group may hinder fluorine removal.^{65, 136} The potential-energy diagram in such a case is probably that represented by the solid line shown in Fig. 7 (B) which implies the non-rate-determining formation of an intermediate σ -complex. Another condition is the use of a reagent with large steric requirements (I^- , PhNHMe). This, however, would render bond-making more difficult to attain as a primary step and lead to a synchronous process of the kind represented by the dotted-line curve of Fig. 7 (B). Under the latter conditions, expectedly unfavorable to the two-step mechanism, Bunnett and Randall¹³⁷ discovered a case of general base catalysis and obtained kinetics consistent with it. However, the occurrence of a less probable termolecular, one-step mechanism has not been excluded.¹³⁸ It is in light of the special conditions just referred to that perhaps the distinction between the two mechanisms in question becomes structurally more significant. In this area of research no examples dealing with heteroaromatic substrates have been reported.

Zollinger's bifunctional catalysis⁵² (Sections II, D, 2, b and III, A) is probably further evidence in favor of the intermediate σ -complex



¹³⁴ P. J. C. Fierens and A. Halleux, *Bull. Soc. Chim. Belges* **64**, 717 (1955).

¹³⁵ G. S. Hammond and L. R. Parks, *J. Am. Chem. Soc.* **77**, 340 (1955).

¹³⁶ R. Bolton, J. Miller, and A. J. Parker, *Chem. Ind. (London)* 1026 (1960).

¹³⁷ J. F. Bunnett and J. J. Randall, *J. Am. Chem. Soc.* **80**, 6020 (1958).

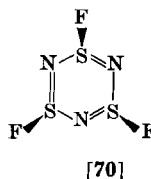
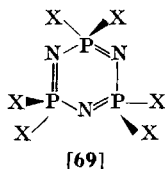
¹³⁸ R. E. Parker, *Advan. Fluorine Chem.* **3**, 63 (1963).

mechanism in heterocyclic chemistry. A synchronous process would imply an effective acid-base interaction in the primary stage of the reaction, which is unlikely to be other than extremely weak due to the very low basicity of cyanuric chloride (Section II, D, 2, a). A much more probable participation of a ring-nitrogen atom would be that starting from the intermediate complex where the ring-nitrogen electron-donor properties have markedly increased [Eq. (18)].

As expected, and shown above, available physical-organic evidence generally indicates similar mechanisms for both heteroaromatic and nitro-activated benzenoid nucleophilic substitution. However, several distinctive features are involved with heterocycles, notably Bank's acid catalysis (*via* acid-base pre-equilibrium, Section II, D, 2, b), the just-mentioned bifunctional catalysis, and peculiar values of the RS^-/RO^- reactivity ratio (Section III, C). Some of these features have not as yet well elucidated. Also, more work is needed to establish "mechanistic ranges," especially with regard to the less frequently used experimental conditions (dipolar aprotic solvents, reagents with large steric requirements, etc.) and with the purely aza-activated substrates, i.e., those not containing auxiliary activating groups (NO_2) which unavoidably tend to obscure the characterization of the behavior of the heterocycle proper.

VI. Inorganic Heteroaromatic Substitution Reactions

The aromaticity of such inorganic ring systems as borazine, the phosphonitrilic halides (**69**), and the thiazyl halides (**70**) has been studied extensively from a theoretical viewpoint.¹³⁹



Many examples of nucleophilic substitutions¹⁴⁰ of the phosphonitrilic halides are known and the first physical-organic papers on the

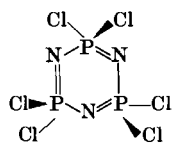
¹³⁹ D. P. Craig, in "Kekulé Symposium on Theoretical Organic Chemistry," London, 1958, p. 20. Butterworths, London, 1959; M. J. S. Dewar, E. A. C. Lucken, and M. A. Whitehead, *J. Chem. Soc.* 2423 (1960); D. P. Craig, M. L. Heffernan, R. Mason, and N. L. Paddock, *ibid.* 1376 (1961).

¹⁴⁰ N. L. Paddock and H. T. Searle, *Advan. Inorg. Chem. and Radiochem.* **1**, 348 (1959); R. A. Shaw, B. W. Fitzsimmons, and B. C. Smith, *Chem. Rev.* **62**, 247 (1962).

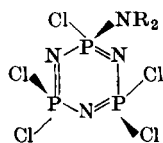
subject began to appear late in 1962.^{141, 142} Here the reaction center is an element in the second period and both the stereochemical conformation and the availability of *d*-orbitals make a synchronous one-step mechanism (S_N2 at phosphorus) less improbable than in the reactions at an aromatic carbon. Furthermore, the tendency to form σ -adducts needs to be ascertained. Since the preliminary results may appear to be contradictory if one has to choose between a one-step and a two-step mechanism, it is convenient to center our attention on the relative importance of bond-making and bond-breaking at this stage of our knowledge.

In hydroxylic solvents, the reaction with aniline follows a bimolecular course but is complicated by competing solvolysis. This is a striking result when compared with the behavior of picryl chloride, which is much more selective with regard to the same reagents (aniline and alcohol), and has been interpreted¹⁴¹ to mean that bond-breaking has made appreciable progress in the rate-determining step of the reaction of phosphonitrilic chloride. Furthermore, the same indication is obtained from the fact that in the reactions of the halides, the fluorine:chlorine ratios are less than one.¹⁴³

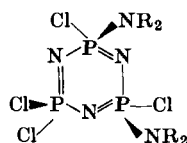
In non-polar solvents, the reaction with piperidine is best represented by a two-term kinetic form indicating a mixed 2nd- and 3rd-order reaction. Also, base catalysis by tri-*n*-butylamine was observed. This kinetic pattern is strongly reminiscent of the results obtained with nitro-activated benzenes.¹⁴⁴ Another interesting result is that stepwise replacement of chlorine atoms by amino groups results in marked



relative rate 500



relative rate 10



relative rate 1

deactivation, although not as strong as that found in *s*-triazine derivatives (Section IV, C, 2). Thus, qualitatively, the reaction appears to be affected by structural changes in the same way as organic

¹⁴¹ J. V. Bailey and R. E. Parker, *Chem. Ind. (London)* 1823 (1962).

¹⁴² B. Capon, K. Hills, and R. A. Shaw, *Proc. Chem. Soc.* 390 (1962).

¹⁴³ F. Seel and J. Langer, *Z. Anorg. Allgem. Chem.* **295**, 316 (1958); A. B. Burg and A. P. Caron, *J. Am. Chem. Soc.* **81**, 836 (1959).

¹⁴⁴ See Ref. 4 in Ref. 142.

heteroaromatic systems. This and the kinetic dependence on the nucleophilic reagent indicate that bond-making is also important in the rate-determining step of the reaction.

What are the details of the reaction mechanism for inorganic aromatic heterocycles? While we are still arguing about aromatic substitutions, we wish to add this new challenge for future investigations.

VII. Appendix: Kinetic Data for Nucleophilic Heteroaromatic Substitution

Interpretations may be ephemeral, but experimental data are permanent. To conserve space, the collection of kinetic data presented here is confined to studies which include the determination of at least one activation parameter. For kinetic studies reporting rate constants at a single temperature the following references should be consulted: 21, 23, 27, 29(b), 30, 31, 33-39, 44, 46, 48, 52, 81, 86, 92, 96, 99, 141, and 142, as well as some of the tables in this review. Among the excluded studies, those involving catalytic phenomena are especially worthy of mention.

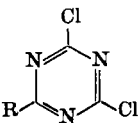
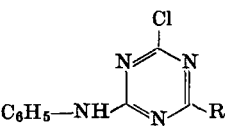
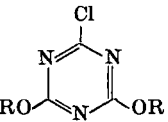
The heterocycles have been arranged in the following sequence: six-membered rings (aza- and polyaza-benzenes, aza- and polyazaphthalenes, etc.) followed by five-membered rings. Derivatives are arranged in alphabetical order according to the substituents.

In the second and third columns, the reagent and solvent, respectively, are entered.

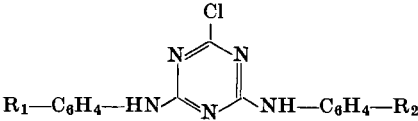
Rate constants (fifth column) usually correspond to one of the temperatures reported in the original papers and may be either experimentally determined values or those calculated from the activation parameters. In the preparation of the present review, the author has normalized a number of rate constants at arbitrary temperatures to permit direct comparisons with other data; these normalized values and temperatures are tabulated (in italics) with the hope that they will offer additional useful information. The rate constants are usually expressed in $\text{liter} \times \text{mole}^{-1} \times \text{sec}^{-1}$; when the values are followed by the symbol (k_1) the units are sec^{-1} . E_a and ΔH^* are in kcal/mole; ΔS^* is in eu.

Compound	Reagent	Solvent
Pyridine derivatives		
2-bromo	piperidine	piperidine
2-chloro	piperidine	piperidine
	piperidine	ethanol
	sodium ethoxide	ethanol
4-chloro	sodium ethoxide	ethanol
2-chloro-3-cyano-4,6-dimethyl-5-nitro	aniline	methanol
2-chloro-3-cyano-6-methyl-5-nitro	aniline	methanol
2-chloro-3-cyano-5-nitro	aniline	methanol
	<i>o</i> -toluidine	methanol
	<i>o</i> -fluoroaniline	methanol
	<i>o</i> -chloroaniline	methanol
	<i>m</i> -chloroaniline	methanol
	<i>p</i> -chloroaniline	methanol
2-chloro-4-methyl-5-nitro	piperidine	ethanol
2-chloro-3-nitro	piperidine	ethanol
	aniline	ethanol
	<i>m</i> -toluidine	ethanol
	<i>p</i> -toluidine	ethanol
	pyridine	ethanol
	3-picoline	ethanol
	4-picoline	ethanol
2-chloro-5-nitro	piperidine	ethanol
	aniline	ethanol
	<i>m</i> -toluidine	ethanol
	<i>p</i> -toluidine	ethanol
	<i>p</i> -anisidine	ethanol
	aniline	methanol
	pyridine	ethanol
	3-picoline	ethanol
	4-picoline	ethanol
4-chloro-3-nitro	water	H ₂ SO ₄ , 6.04 <i>M</i> in H ₂ O
	pyridine	ethanol
	3-picoline	ethanol
	4-picoline	ethanol
2-chloro, <i>N</i> -oxide	piperidine	methanol
4-chloro, <i>N</i> -oxide	piperidine	methanol
2-iodo-5-nitro	water	H ₂ SO ₄ , 6.04 <i>M</i> in H ₂ O
Pyridinium ion derivatives		
2-cyano- <i>N</i> -methyl	NaOH	water
3-cyano- <i>N</i> -methyl	NaOH	water
4-cyano- <i>N</i> -methyl	NaOH	water
Pyrimidine derivatives		
6- <i>t</i> -butyl-4-chloro	piperidine	ethanol
2-chloro	piperidine	ethanol
	piperidine	ethanol

t, °C	10 ⁴ k	E _a	log A	ΔH*	−ΔS*	References
75.2	0.219(<i>k</i> ₁)	16.4	—	—	—	98
75.2	0.0234(<i>k</i> ₁)	17.1	—	—	42.2	43
75.2	0.0012	19.9	5.5	19.1	35.8	20, 42
20	0.000022	26.8	—	26.2	9.2	20
75.2	0.2163	20.9	—	20.2	22.3	20
30	0.415	12.4	4.56	11.8	39.6	47
30	31.6	10.5	5.07	9.9	37.2	47
10	38.5	9.8	5.18	9.2	36.7	47
10	2.72	13.3	6.7	—	—	47
10	0.558	12.5	5.13	—	—	47
10	0.03	13.9	5.23	—	—	47
10	1.8	12.1	5.6	—	—	47
10	6.56	10.9	5.22	—	—	47
30	12.6	12.4	6.0	—	—	42
55	184.1	12.0	6.2	—	—	42
55	0.169	14.5	5.0	—	—	26
55	0.224	14.4	5.0	—	—	58
55	0.50	13.9	4.9	—	—	26
55	0.0103	18.7	6.3	—	—	26
55	0.0181	18.5	6.6	—	—	58
55	0.0315	17.4	6.1	—	—	58
55	281.8	11.5	6.1	—	—	42
30	0.02213	13.1	3.8	6.1	22.8	26, 58
55	0.16	12.9	3.8	5.9	22.8	26, 58
55	0.343	12.7	3.9	5.3	23.2	26, 58
55	1.012	11.5	3.5	—	—	26
30	0.02449	14.9	5.06	14.3	37.2	47
55	0.0197	18.1	6.3	8.7	11.0	26, 58
55	0.040	17.9	6.6	8.1	—	58
55	0.0611	17.5	6.5	7.5	—	58
80.5	2.49(<i>k</i> ₁)	21.7	—	—	—	8
55	0.321	16.9	6.8	—	—	26, 58
55	0.398	15.6	6.0	—	—	58
55	0.664	15.1	5.9	—	—	58
80	3.70(<i>k</i> ₁)	14.4	5.49	—	—	73
80	1.02(<i>k</i> ₁)	15.2	5.45	—	—	73
82.1	0.826(<i>k</i> ₁)	22.9	—	—	—	8
25.2	517,000	14.36	12.22	13.77	4.61	25
25.2	2,810	14.13	9.76	13.54	15.87	25
25.2	18,400	14.88	11.14	14.29	9.55	25
20	4.47	11.0	4.9	—	—	94
49.9	24.3	10.6	—	—	37.2	43
75.2	80.6	12.4	5.7	—	—	42

Compound	Reagent	Solvent
2-chloro	piperidine sodium ethoxide morpholine	petr. ether ethanol ethanol
4-chloro	piperidine	ethanol
2-chloro-4,6-dimethyl	piperidine morpholine	ethanol ethanol
2-chloro-4-methyl	piperidine morpholine	ethanol ethanol
4-chloro-2-methyl	piperidine morpholine	ethanol ethanol
4-chloro-6-methyl	piperidine morpholine	ethanol ethanol
Pyrazine derivatives		
2-chloro	piperidine	toluene
2,4-Dichloro-6-substituted- <i>s</i> -triazines		
amino	<i>p</i> -toluidine	tetrahydrofuran
anilino	<i>p</i> -toluidine	tetrahydrofuran
<i>N,N</i> -dimethylamino	<i>p</i> -toluidine	tetrahydrofuran
<i>N</i> -methylamino	<i>p</i> -toluidine	tetrahydrofuran
<i>N</i> -methylanilino	<i>p</i> -toluidine	tetrahydrofuran
<i>N</i> -morpholino	<i>p</i> -toluidine	tetrahydrofuran
<i>m</i> -toluidino	<i>p</i> -toluidine	tetrahydrofuran
<i>p</i> -toluidino	<i>p</i> -toluidine	tetrahydrofuran
2-Anilino-4-chloro-6-substituted- <i>s</i> -triazines		
amino	benzylamine	tetrahydrofuran
anilino	benzylamine	tetrahydrofuran
chloro	benzylamine	tetrahydrofuran
<i>N,N</i> -dimethylamino	benzylamine	tetrahydrofuran
<i>N</i> -methylamino	benzylamine	tetrahydrofuran
2-Chloro-4,6-diaryloxy- <i>s</i> -triazines		
<i>p</i> -chlorophenyl	aniline	acetone
phenyl	aniline	acetone
<i>p</i> -tolyl	aniline	acetone

t, °C	10 ⁴ k	E _a	log A	ΔH*	-ΔS*	References
75.2	11.75	11.5	—	—	44.4	43
20	16.3	16.9	—	16.3	15.7	20
30	1.52	12.3	5.0	—	—	42
20	~14	~10.5	~5	—	—	94
30	1.13	12.1	4.8	—	—	42
30	0.281	12.6	4.5	—	—	42
30	2.80	12.5	5.4	—	—	42
30	0.691	13.0	5.2	—	—	42
30	30.0	10.6	5.1	—	—	42
30	7.71	10.7	4.6	—	—	42
30	21.4	11.0	5.2	—	—	42
30	5.55	11.1	4.7	—	—	42
75.2	0.1	13.2	—	—	50.4	43
40	20.2	13.1	—	—	31	50
40	240	8.0	—	—	43	50
40	19.5	10.0	—	—	43	50
40	17.5	10.1	—	—	41	50
40	95.1	9.2	—	—	41	50
40	62.0	10.0	—	—	39	50
40	221	8.4	—	—	41	50
40	170	8.0	—	—	43	50
40	0.652	14.7	—	—	33	49
40	3.24	12.0	—	—	39	49
40	9,310	7.87	—	—	36	49
40	0.544	14.0	—	—	37	49
40	0.463	14.0	—	—	36	49
35	128	8.8	6.13	—	—	59
35	38	9.6	6.16	—	—	59
35	25	10.3	6.48	—	—	59

Compound	Reagent	Solvent
2,4-Bis(substituted-anilino)-6-chloro-s-triazines		
	 $\text{R}_1\text{—C}_6\text{H}_4\text{—HN} \begin{array}{c} \text{Cl} \\ \\ \text{N} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{N} \end{array} \text{NH—C}_6\text{H}_4\text{—R}_2$	
<i>p</i> -chloro	benzylamine	tetrahydrofuran
<i>p</i> -chloro- <i>p</i> '-methyl	benzylamine	tetrahydrofuran
<i>p</i> -chloro- <i>m</i> '-nitro	benzylamine	tetrahydrofuran
<i>p,p</i> '-dichloro	benzylamine	tetrahydrofuran
<i>p,p</i> '-dimethoxy	benzylamine	tetrahydrofuran
<i>m,m</i> '-dimethyl	benzylamine	tetrahydrofuran
<i>p,p</i> '-dimethyl	benzylamine	tetrahydrofuran
<i>m,m</i> '-dinitro	benzylamine	tetrahydrofuran
<i>p</i> -methoxy	benzylamine	tetrahydrofuran
<i>m</i> -methyl	benzylamine	tetrahydrofuran
<i>p</i> -methyl	benzylamine	tetrahydrofuran
<i>m</i> -nitro	benzylamine	tetrahydrofuran
Quinoline derivatives		
4-acetyl-2-chloro	sodium methoxide	methanol
2-bromo	piperidine	piperidine
	piperidine	piperidine
3-bromo	piperidine	piperidine
4-bromo	piperidine	70% ethanol
	piperidine	95% ethanol
5-bromo	piperidine	piperidine
6-bromo	piperidine	piperidine
	piperidine	piperidine
7-bromo	piperidine	piperidine
8-bromo	piperidine	piperidine
	piperidine	piperidine
6-bromo-4-chloro	sodium methoxide	methanol
7-bromo-4-chloro	sodium methoxide	methanol
4-bromo, <i>N</i> -oxide	piperidine	70% ethanol
	piperidine	95% ethanol
2-chloro	piperidine	piperidine
	piperidine	ethanol
	piperidine	methanol
	piperidine	petr. ether
	piperidine	toluene
	piperidine	toluene
	sodium ethoxide	ethanol
	sodium methoxide	methanol
4-chloro	piperidine	piperidine
	piperidine	piperidine
	piperidine	70% ethanol

t, °C	10 ⁴ k	E _a	log A	ΔH*	-ΔS*	References
40	3.24	11.9	—	—	39	28
40	5.76	11.9	—	—	38	28
40	4.27	11.8	—	—	38	28
40	26.0	11.4	—	—	36	28
40	10.1	11.2	—	—	38	28
40	1.20	12.8	—	—	38	28
40	2.15	12.7	—	—	37	28
40	1.79	12.4	—	—	38	28
40	60.3	10.3	—	—	38	28
40	2.02	12.6	—	—	37	28
40	2.80	12.1	—	—	38	28
40	2.52	12.4	—	—	38	28
40	14.1	10.9	—	—	39	28
75.2	47.41	20.5	—	—	12.3	104
75.2	5.83(<i>k</i> ₁)	13.8	—	—	—	98
0.0	0.065(<i>k</i> ₁)	12.8	—	—	36(ΔV*)	24
200	0.132(<i>k</i> ₁)	21.6	—	—	43.6	18
100	0.75	—	—	17.0	32	32
100	0.59	—	—	14.5	39	32
200	0.037(<i>k</i> ₁)	22.0	—	—	44.6	18
200	0.08(<i>k</i> ₁)	23.9	—	—	39.1	18
184	0.032(<i>k</i> ₁)	24.4	—	—	64(ΔV*)	24
200	0.29(<i>k</i> ₁)	21.6	—	—	41.5	18
125.4	0.0074(<i>k</i> ₁)	21	—	—	41(ΔV*)	24
200	0.56(<i>k</i> ₁)	23.3	—	—	37.2	18
75.2	21.41	21.4	—	—	11.7	19
75.2	21.77	20.4	—	—	14.2	103
100	15.6	—	—	12.4	36	32
100	8.87	—	—	10.7	44	32
75.2	1.71(<i>k</i> ₁)	13.8	—	—	43.2	98, 18
75.2	0.1084	15.6	—	14.9	38.9	20
86.5	0.26	16.8	—	—	34.9	29
75.2	0.027	14.9	—	—	44	18
75.2	0.091	12.9	—	—	45.2	18
86.5	0.041	18.2	—	—	35.1	29
20	0.0063	23.1	10.9	22.4	10.7	20, 122
75.2	2.22	24.2	—	23.9	7.0	87
75.2	0.037(<i>k</i> ₁)	16.1	—	—	44.5	18
70.08	0.032(<i>k</i> ₁)	14.94	7.57	—	—	110
100	0.39	—	—	20.6	24	32

Compound	Reagent	Solvent
4-chloro	piperidine sodium ethoxide sodium methoxide	95% ethanol ethanol methanol
2-chloro-4-cyano	sodium methoxide	methanol
4-chloro-6-dimethylamino	sodium methoxide	methanol
2-chloro-4-ethoxy	sodium methoxide	methanol
4-chloro-2-ethoxy	sodium methoxide	methanol
4-chloro-6-ethoxy	sodium methoxide	methanol
4-chloro-6-fluoro	sodium methoxide	methanol
4-chloro-7-fluoro	sodium methoxide	methanol
2-chloro-4-methoxy	sodium methoxide	methanol
4-chloro-2-methoxy	sodium methoxide	methanol
4-chloro-6-methoxy	sodium methoxide	methanol
4-chloro-7-methoxy	sodium methoxide	methanol
2-chloro-4-methyl	sodium methoxide	methanol
2-chloro-7-methyl	sodium methoxide	methanol
4-chloro-2-methyl	sodium methoxide	methanol
4-chloro-6-methyl	piperidine sodium methoxide	piperidine methanol
4-chloro-8-methyl	piperidine	piperidine
2-chloro-4-methylthio	sodium methoxide	methanol
4-chloro-2-methylthio	sodium methoxide	methanol
4-chloro-6-methylthio	sodium methoxide	methanol
2-chloro-6-nitro	sodium methoxide	methanol
4-chloro-5-nitro	sodium methoxide	methanol
4-chloro-6-nitro	sodium methoxide	methanol
4-chloro-7-nitro	sodium methoxide	methanol
4-chloro, <i>N</i> -oxide	piperidine piperidine	70% ethanol 95% ethanol
2-chloro-4-trifluoromethyl	sodium methoxide	methanol
4-chloro-2-trifluoromethyl	sodium methoxide	methanol
2,4-dichloro ^a	sodium methoxide	methanol
2,4-dichloro ^b	sodium methoxide	methanol
2,6-dichloro	sodium methoxide	methanol
2,7-dichloro	sodium methoxide	methanol
4,6-dichloro	piperidine sodium methoxide	piperidine methanol
4,7-dichloro	piperidine sodium methoxide	piperidine methanol
4,8-dichloro	piperidine	piperidine
4-iodo	piperidine piperidine	70% ethanol 95% ethanol
4-iodo, <i>N</i> -oxide	piperidine piperidine	70% ethanol 95% ethanol
Isoquinoline derivatives		
1-chloro	piperidine piperidine	piperidine ethanol

^a Reactivity at position 2.^b Reactivity at position 4.

t, °C	10 ⁴ k	E _a	log A	ΔH*	−ΔS*	References
100	0.21	—	—	16.3	37	32
20	0.0065	20.4	9.0	19.7	19.6	20, 122
75.2	2.47	21.2	—	20.3	17.2	19, 87
75.2	1,190	21.1	—	20.4	4.7	87
75.2	0.0721	23.1	—	—	18.1	19
75.2	0.478	19.5	—	18.7	24.9	87
75.2	0.159	21.3	—	20.4	22.3	87
75.2	0.472	23.6	—	—	12.9	19
75.2	5.25	21.7	—	—	13.7	19
75.2	12.36	18.9	—	—	20.0	103
75.2	0.486	20.0	—	19.3	23.1	87
75.2	0.143	22.7	—	22.0	18.0	87
75.2	0.529	22.9	—	—	14.7	19
75.2	1.44	21.6	—	—	16.3	103
75.2	0.877	21.4	—	20.8	17.8	87
75.2	1.13	23.9	—	—	10.2	104
75.2	0.776	22.1	—	21.4	16.2	87
70.08	0.01(k ₁)	16.44	8.03	—	—	110
75.2	0.957	22.7	—	—	14.2	19
70.08	0.016(k ₁)	14.0	6.68	—	—	110
75.2	1.94	21.8	—	21.0	15.4	87
75.2	1.17	18.7	—	18.0	22.2	87
75.2	3.05	22.2	—	—	13.2	19
75.2	1,793	15.0	—	—	21.0	104
75.2	17.9	19.0	—	—	19.0	105
75.2	1,058	16.9	—	—	16.6	19
75.2	257.9	19.4	—	—	12.3	103
100	10.1	—	—	10.8	42	32
100	5.82	—	—	7.96	52	32
75.2	302.4	17.24	—	—	18.26	104
75.2	167.7	18.5	—	—	15.7	103
75.2	39.4	19.6	—	18.9	15.6	87
75.2	74.7	20.0	—	19.4	13.0	87
75.2	13.79	20.2	—	—	15.9	104
75.2	23.6	21.1	—	—	12.4	104
70.08	0.167(k ₁)	15.4	8.58	—	—	110
75.2	16.8	21.0	—	—	13.2	19
70.08	0.265(k ₁)	13.75	7.49	—	—	110
75.2	21.44	18.1	—	—	21.1	103
70.08	0.33(k ₁)	12.6	6.9	—	—	110
100	0.37	—	—	16.6	35	32
100	0.32	—	—	13.2	44	32
100	3.51	—	—	10.6	46	32
100	2.61	—	—	10.6	47	32
75.2	1.03(k ₁)	13.5	—	—	44.7	43
20	0.0025	14.5	—	13.8	41.9	20

Compound	Reagent	Solvent
1-chloro	sodium ethoxide	ethanol
3-chloro	sodium ethoxide	ethanol
Cinnoline derivatives		
4-chloro	sodium ethoxide	ethanol
	sodium methoxide	methanol
6-chloro	sodium methoxide	methanol
Quinazoline derivatives		
2-chloro	piperidine	ethanol
	sodium ethoxide	ethanol
4-chloro	piperidine	ethanol
Quinoxaline derivatives		
7-bromo-2-chloro	sodium methoxide	methanol
2-chloro	piperidine	ethanol
	piperidine	toluene
	sodium ethoxide	ethanol
	sodium methoxide	methanol
2-chloro-7-methoxy	sodium methoxide	methanol
2-chloro-7-methyl	sodium methoxide	methanol
2-chloro-7-trifluoromethyl	sodium methoxide	methanol
2,6-dichloro	sodium methoxide	methanol
2,7-dichloro	sodium methoxide	methanol
Phthalazine derivatives		
1-chloro	piperidine	ethanol
	sodium ethoxide	ethanol
Acridine derivatives		
9-chloro	piperidine	toluene
	sodium ethoxide	ethanol
Furan derivatives		
2-bromo	piperidine	piperidine
	sodium methoxide	methanol
2-bromo-5-carbomethoxy	sodium methoxide	methanol
2-chloro	piperidine	piperidine
2-chloro-5-CON(CH ₂) ₅	piperidine	piperidine
2-iodo	piperidine	piperidine
2-iodo-5-methyl	piperidine	piperidine
Thiophene derivatives		
2-bromo-3-nitro	piperidine	piperidine
	piperidine	ethanol
2-bromo-5-nitro	piperidine	piperidine
	piperidine	ethanol
3-bromo-2-nitro	piperidine	piperidine
3-bromo-5-nitro	piperidine	piperidine
2-chloro-3-nitro	piperidine	ethanol

t, °C	10 ⁴ k	E _a	log A	ΔH*	-ΔS*	References
20	0.007	22.5	—	21.8	12.3	20
20	0.00000012	32.4	—	31.6	0.7	20
20	47.7	15.8	—	15.2	17.3	20
75.2	2,961	15.8	—	—	17.7	103
5	41.27	15.1	—	—	16.8	103
20	4.79	11.1	—	10.5	37.8	20
20	29.8	16.8	—	16.2	15.9	20
20	31,000	7.0	—	6.6	37.2	43, 20
5	177.3	14.6	—	—	15.5	104
20	0.636	11.3	—	10.8	40.9	20
75.2	1.32	11.4	—	—	46.2	43
20	82.8	15.4	—	14.8	18.2	20
5	13.6	16.7	—	—	13.6	104
5	4.12	16.6	—	—	16.2	104
5	5.89	16.9	—	—	14.3	104
5	552	15.1	—	—	11.7	104
5	77.42	14.8	—	—	16.6	104
5	152.1	16.6	—	—	8.9	104
20	0.2	11.8	—	11.1	42.0	20
20	18.6	16.5	—	15.9	16.9	20
75.2	0.27	14.5	—	—	40.5	43
20	0.62	17.6	—	17.0	20.0	20
200	0.063(<i>k</i> ₁)	21.7	8.4	—	39.1	22, 120
200	0.31	36.8	—	—	4.48	22
200	4,850	24.5	—	—	10.3	22
200	0.0073(<i>k</i> ₁)	21.9	7.8	—	42.1	120
200	0.38(<i>k</i> ₁)	17.2	—	—	37.1	120
200	0.131(<i>k</i> ₁)	30.8	12.9	—	18.8	120
200	0.06(<i>k</i> ₁)	26.6	10.6	—	29.1	120
20	145(<i>k</i> ₁)	9.76	7.2	—	—	121
19.9	1.29	13.7	6.3	—	—	33
20	6.43(<i>k</i> ₁)	9.86	5.9	—	—	121
19.9	0.258	15.7	7.1	—	—	33
20	600(<i>k</i> ₁)	7.6	6.2	—	—	121
20	0.2(<i>k</i> ₁)	25.8	16.33	—	—	121
19.9	2.26	14.8	7.4	—	—	33

Compound	Reagent	Solvent
2-chloro-5-nitro	piperidine	ethanol
2-iodo-3-nitro	piperidine	ethanol
2-iodo-5-nitro	piperidine	ethanol
Benzothiophene derivatives		
2-bromo	piperidine	piperidine
Thiazole derivatives		
2-chloro	piperidine	piperidine
Benzothiazole derivatives		
2-chloro	piperidine	toluene
	sodium methoxide	methanol
	ammonia	liquid ammonia
2-chloro-6-methoxy	sodium methoxide	methanol
2-chloro-5-methyl	sodium methoxide	methanol
2-chloro-6-methyl	sodium methoxide	methanol
2-chloro-4-nitro	sodium methoxide	methanol
2-chloro-5-nitro	sodium methoxide	methanol
2-chloro-6-nitro	sodium methoxide	methanol
2,5-dichloro	sodium methoxide	methanol
2,6-dichloro	sodium methoxide	methanol

t, °C	10 ⁴ k	E _a	log A	ΔH*	−ΔS*	References
19.9	0.431	16.4	7.9	—	—	33
19.9	0.142	16.4	7.4	—	—	33
19.9	0.0309	18.6	8.4	—	—	33
75.2	0.000044(k ₁)	20.2	—	—	46.5	123
75.2	0.816(k ₁)	13.8	—	—	44.5	98, 43
75.2	4.15	11.0	—	—	44.6	43
25	5.5	16.9	9.2	—	—	122
30	0.11(k ₁)	13.7	—	—	—	34
25	0.893	18.7	9.7	—	—	122
25	3.74	17.8	9.6	—	—	122
25	1.97	18.3	9.7	—	—	122
25	1,320	16.3	11.1	—	—	122
25	878	15.4	10.2	—	—	122
25	2,800	14.2	9.9	—	—	122
25	63.7	15.8	9.4	—	—	122
25	32.5	16.0	9.3	—	—	122

ACKNOWLEDGMENTS

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Pentazoles*

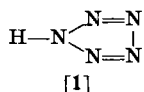
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I. Introduction

The classical age of preparative organic chemistry saw the exploration of the extensive field of five-membered heterocyclic aromatic systems. The stability of these systems, in contrast to saturated systems, is not necessarily affected by the accumulation of neighboring heteroatoms. In the series pyrrole, pyrazole, triazole, and tetrazole an increasing stability is observed in the presence of electrophiles and oxidants,¹ and a natural next step was to attempt the synthesis of pentazole (**1**). However, pentazole has eluded the manifold and continual efforts²⁻⁹ to synthesize and isolate it.



*The author is indebted to Dr. A. R. Katritzky and Mr. R. Srb for their linguistic help.

¹ R. Huisgen, *Angew. Chem.* **72**, 359 (1960).

² A. Hantzsch, *Ber.* **36**, 2056 (1903).

³ O. Dimroth and G. de Montmollin, *Ber.* **43**, 2904 (1910).

⁴ J. Lifschitz, *Ber.* **48**, 410 (1915).

⁵ T. Curtius, A. Darapsky, and E. Müller, *Ber.* **48**, 1614 (1915).

⁶ K. Clusius and H. Hürzeler, *Helv. Chim. Acta* **37**, 798 (1954).

⁷ J. P. Horwitz and V. A. Grakauskas, *J. Am. Chem. Soc.* **79**, 1249 (1957).

⁸ R. Criegee and A. Rimmelin, *Chem. Ber.* **90**, 414 (1957).

⁹ K. Clusius and F. Endtinger, *Helv. Chim. Acta* **41**, 1823 (1958).

In this connection, it is remarkable that in 1893 Noelting and Michel¹⁰ produced, albeit unknowingly, arylpentazoles (2) while generating aryl azides (3) from aryldiazonium compounds and sodium azide.

II. The Characterization of Arylpentazoles

A. THE ISOLATION OF ARYLPENTAZOLES

Arylpentazoles can be prepared by adding an aqueous solution of azide to a mixture of an aryldiazonium chloride, aqueous methanol, and petroleum ether at -40 to -20° with stirring.¹¹⁻¹³ The pure arylpentazole (see Table I) crystallizes from the two-phase reaction mixture; the inorganic impurities remain in the aqueous methanol and the organic impurities in the petroleum ether.

TABLE I
CRYSTALLINE ARYLPENTAZOLES

Compound	Yield, %	Decomposition point, °C
Phenylpentazole	27	-5-3
<i>p</i> -Tolylpentazole	32	2-5
<i>p</i> -Chlorophenylpentazole	21	8-10
<i>p</i> -Methoxyphenylpentazole	38	13-15
<i>p</i> -Ethoxyphenylpentazole	42	26-29
<i>p</i> -Dimethylaminophenylpentazole	52	50-54

B. THE CHEMICAL AND PHYSICAL PROPERTIES OF ARYLPENTAZOLES

1. The Thermal Instability of Arylpentazoles

Arylpentazoles are colorless crystalline substances which are stable at temperatures below -20° but decompose at room temperature, sometimes exploding. *p*-Dimethylaminophenylpentazole is an exception; the pure compound is of light yellow color and can be kept at room temperature for some hours.

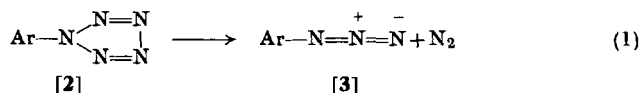
¹⁰ E. Noelting and O. Michel, *Ber.* **26**, 86 (1893).

¹¹ I. Ugi, H. Perlinger, and L. Behringer, *Chem. Ber.* **91**, 2324 (1958).

¹² I. Ugi, Habilitation Thesis, University of Munich, 1959.

¹³ H. Perlinger, Doctoral Thesis, University of Munich, 1959.

In solution arylpentazoles decompose spontaneously by a first-order reaction (see Section III), yielding arylazide and nitrogen quantitatively [Eq. (1)]. The stability of phenylpentazole in solution increases



with the dielectric constant of the solvent, as is shown by the effect of the solvent upon the rate of decomposition (see Table II). Therefore, one may infer that the transition state of the decomposition is less polar than phenylpentazole (see Section III, A, 3). The activation energy for the decomposition of phenylpentazole is 21.4 kcal/mole.¹⁴

TABLE II
THE DECOMPOSITION OF PHENYLPENTAZOLE IN VARIOUS
SOLVENTS^a

Solvent	$k_{r,d} \times 10^4 (\text{sec}^{-1})^b$
<i>n</i> -Hexane	45.2
Carbon tetrachloride	34.0
<i>n</i> -Butanol	16.9
Toluene	12.4
Tetrahydrofuran	10.4
Methanol	9.8
Chloroform	8.9
Acetone	7.7
Acetonitrile	4.1
Formic acid	2.3
Carbon tetrachloride/acetonitrile (20) ^c	15.1
Carbon tetrachloride/acetonitrile (40)	11.2
Carbon tetrachloride/acetonitrile (60)	8.0
Carbon tetrachloride/acetonitrile (80)	7.1
Methanol/water (50)	5.7
Acetic acid/water (25)	5.8

^a I. Ugi, H. Perlinger, and L. Behringer, *Chem. Ber.* **91** 2324 (1958).

^b The subscripts *r* and *d* refer to ring and decomposition, respectively.

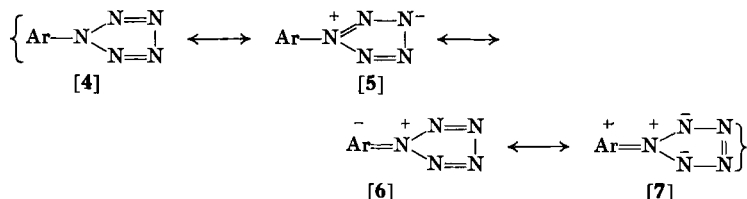
^c Mole-% of the second component.

¹⁴ R. Huisgen and I. Ugi, (a) *Angew. Chem.* **68**, 705 (1956); (b) *Chem. Ber.* **90**, 2914 (1957).

Considering the low energy level of elemental nitrogen, the decomposition enthalpy of *p*-ethoxyphenylpentazole (5.4 kcal/mole)¹¹ indicates the high resonance energy of the pentazole system.

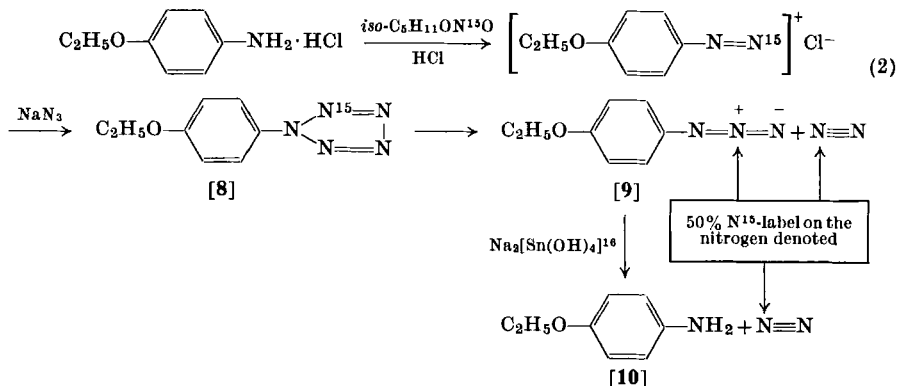
2. The UV-Absorption of Arylpentazoles

The pronounced bathochromic effect of electron-donating *para*-substituents in the benzene ring of phenylpentazole derivatives¹¹ reveals a strong mutual resonance interaction between the isocyclic and heterocyclic moieties (phenylpentazole: λ_{\max} 249 m μ , ϵ_{\max} 7,100; *p*-ethoxyphenylpentazole: λ_{\max} 272 m μ , ϵ_{\max} = 12,300; *p*-dimethylaminophenylpentazole: λ_{\max} 329 m μ , ϵ_{\max} = 14,900). Thus, when strongly electron-donating substituents are present in the benzene ring, one must consider the possibility that not only structures 4–6 but also those corresponding to formula 7 play a part in the resonance of arylpentazoles, analogous to the resonance in *p*-nitraniline.



3. Evidence for the Structure of Arylpentazoles

The structure of *p*-ethoxyphenylpentazole was ascertained through N¹⁵-labeling according to Eq. (2).¹⁵ The data in Table III agree



¹⁵ I. Ugi, H. Perlinger, and L. Behringer, *Chem. Ber.* **92**, 1864 (1959).

¹⁶ I. Ugi, H. Perlinger, and L. Behringer, *Chem. Ber.* **91**, 2330 (1958).

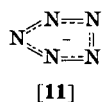
satisfactorily with the assumed structure of *p*-ethoxyphenylpentazole. Although the results of the N^{15} -experiment could also be explained on the basis of a dimer of *p*-ethoxyphenylpentazole containing a ten-membered nitrogen ring, such an improbable structure was ruled out by the molecular weight.¹⁵

TABLE III
 N^{15} MASS BALANCE FOR EQUATION (2)

Source of N^{15}	Calculated, %	Found, %
<i>Iso</i> -amyl nitrite	—	100
Nitrogen ($8 \rightarrow 9 + N_2$)	25.0	24.4
Nitrogen ($9 \rightarrow 10 + N_2$)	25.0	25.0

4. Attempts to Convert Arylpentazoles into Pentazole

Unsubstituted pentazole (11) would be expected to be a strong acid with a highly "aromatic" anion (11) which could possibly form ferrocene analogs such as $M^{II}(N_5)_2$, where M^{II} represents a divalent metal

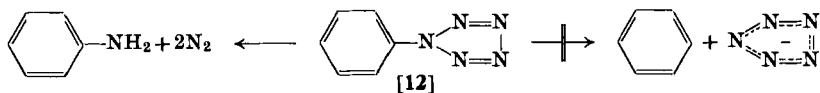


ion. Unfortunately it has not been possible to investigate the properties of unsubstituted pentazole since neither oxidative degradation of the carbocyclic moiety nor reductive cleavage of the N—C bond converted arylpentazoles into pentazole. Ozonization of *p*-dimethylamino-phenylpentazole in methylene chloride at approximately -60° causes decomposition of both the substituted benzene and the pentazole ring.^{13, 17} Attempted cleavage of the N—C bond of phenylpentazole (12) by reduction with sodium in liquid ammonia¹⁸ led to destruction of the pentazole ring¹⁷; aniline and nitrogen were formed, presumably

¹⁷ I. Ugi, *Angew. Chem.* **73**, 172 (1961).

¹⁸ The easy cleavage by reduction of the N—C bond in isocyanides, which was recently observed by I. Ugi and F. Bodesheim [*Chem. Ber.* **94**, 1157 (1961)], stimulated this experiment.

via a 2,3-dihydro intermediate. A relevant analogy would seem to be the reductive degradation of the tetrazole ring.²⁰

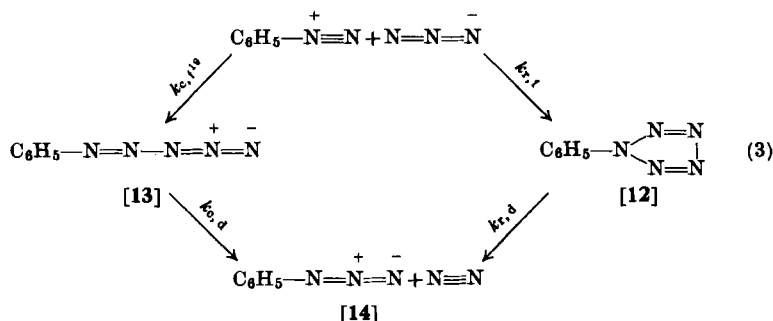


III. The Formation and Decomposition of Arylpentazoles

A. THE RELATIONSHIP OF BENZENEDIAZOAZIDE AND PHENYL-PENTAZOLE

1. Kinetic Evidence

Upon mixing solutions of benzenediazonium chloride and lithium azide, phenylpentazole (12) and covalent benzenediazoazide (13) are instantly formed from the ions [Eq. (3)]. The resulting intermediates



12 and 13 decompose, though at different rates ($k_{r,d} \ll k_{c,d} \ll k_{r,f}$, $k_{c,f}$ ¹⁹), to yield the same end products, phenylazide (14) and nitrogen.¹⁴ For example, the addition of lithium azide in methanol to a methanol solution of benzenediazonium chloride at -25° liberates nitrogen, to the extent of 70% (V_c ¹⁹) of the assumed total, by a rapid first-order reaction. The remaining 30% (V_r ¹⁹) of the nitrogen is set free by a first-order reaction, at a measurable rate, only upon increasing the temperature above -10° . As expected, $k_{r,f}$ and $k_{c,f}$ as well as the ratio $Q_{c,r} = V_c/V_r = k_{c,f}/k_{r,f}$ (see also Section III, A, 3) are dependent upon the temperature and the solvent but are almost independent of the

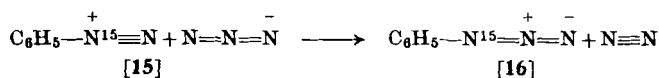
¹⁹ The subscripts *c*, *r*, *f*, *d*, and *i* denote chain, ring, formation, decomposition, and isomerization, respectively. V_c and V_r are the amounts of nitrogen derived from the arenediazoazide and arylpentazole, respectively.

²⁰ R. O. Roblin, J. H. Williams, P. S. Wimek, and J. P. English, *J. Am. Chem. Soc.* **62**, 2002 (1940).

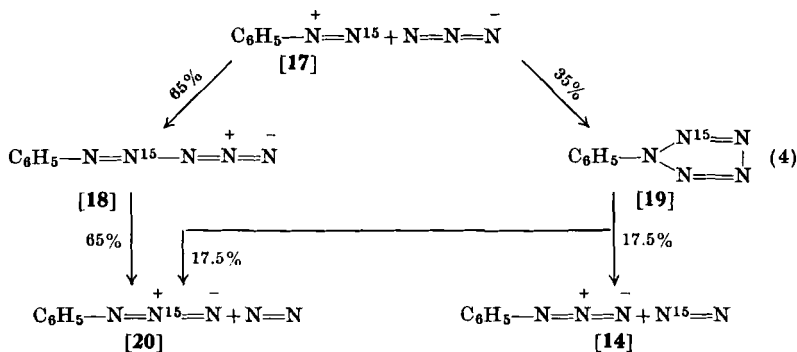
concentrations of the reactants. A low temperature and a highly polar solvent favor the formation of phenylpentazole in preference to benzenediazoazide (low value of $Q_{c,r}$). At 0° in water one finds $Q_{c,r} = 65/35 = 1.86$ and in methanol $Q_{c,r} = 2.70$.^{12, 14b}

2. The Reaction between Azide and Benzenediazonium- $[\beta\text{-N}^{15}]$ Ions

a. *The Distribution of the N^{15} -Label in the End Products.* Clusius and Hürzeler⁶ observed that phenyl azide- $[\alpha\text{-N}^{15}]$ (16) and unlabeled nitrogen are formed by the union of unlabeled azide and isotopically unrearranged²¹ benzenediazonium- $[\alpha\text{-N}^{15}]$ ions (15). They concluded



that the reaction does not proceed by a Sandmeyer-type²² exchange of the diazonium and azide groups. Further, they demonstrated the following N^{15} -distribution in the products of the reaction of benzenediazonium- $[\beta\text{-N}^{15}]$ chloride (17) with sodium azide: 85% of the N^{15} -label is on the middle nitrogen ($\beta\text{-N}^{15}$) of the generated phenylazide (14 + 20) and 15% is in the liberated nitrogen. The simplest explanation of this phenomenon, which is in accord with kinetic results ($Q_{c,r} = 65/17.5 + 17.5$; see Section III, A, 1), can be summarized by the reaction mechanism shown in Eq. (4).^{14b}



b. *The Separate N^{15} -Analysis of the Nitrogen Generated from Phenylpentazole- $[\beta\text{-N}^{15}]$ and Benzenediazoazide- $[\beta\text{-N}^{15}]$.* Upon reacting benzenediazonium- $[\beta\text{-N}^{15}]$ chloride with lithium azide at -25° in

²¹ J. M. Insole and E. S. Lewis, *J. Am. Chem. Soc.* **85**, 122 (1963).

²² H. H. Hodgson, *Chem. Rev.* **40**, 251 (1947).

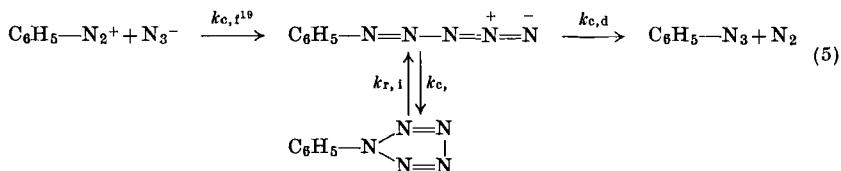
methyl glycol, 74% unlabeled nitrogen is liberated rapidly by the decomposition of benzenediazoazide- $[\beta\text{-N}^{15}]$ (**18**). The remaining 26 mole-% of nitrogen is liberated from phenylpentazole- $[\beta\text{-N}^{15}]$ (**19**) at 0–10°; the latter amount of nitrogen is labeled to the extent of 25%, in accordance with the equivalence of N-2 and N-5 in phenylpentazole [cf. Eq. (4)].^{14b, 23} An analogous study of the reaction of *p*-ethoxybenzenediazonium- $[\beta\text{-N}^{15}]$ chloride with lithium azide gave similar results. Thus, it has been shown unequivocally that arenediazoazides and arylpentazoles are intermediates in the formation of aryl azides and nitrogen from the reaction of azide and aryl diazonium ions.

3. The Mechanism of Formation and Decomposition of Phenylpentazole

The formation and decomposition of benzenediazoazide and phenylpentazole can be described by a mechanism alternative to the one discussed in Section III, A, 1 [Eq. (3)]. In contrast to the tacitly assumed independent formation and decomposition of phenylpentazole, e.g. one-step four-centered processes as described by **21** and **22**,



and benzenediazoazide, one could also infer from the data a mechanism in which benzenediazoazide is an intermediate in both the formation and decomposition [Eq. (5)].



Neither N^{15} -labeling, nor kinetic measurements, nor theoretical reasoning on the basis of MO-calculations²⁴ enable one to rule out either of these alternatives [cf. Eqs. (3) and (5)]. This problem obviously requires an unconventional approach, and a "two-phase experiment"^{12, 25} seems to provide the basis for discriminating.

²³ I. Ugi, R. Huisgen, K. Clusius, and M. Vecchi, *Angew. Chem.* **68**, 753 (1956).

²⁴ J. D. Roberts, *Chem. Ber.* **94**, 273 (1961).

²⁵ I. Ugi, *Tetrahedron* **19**, 1801 (1963).

In 80% aqueous methanol (phase I) at -30° benzenediazonium chloride and lithium azide react to form benzenediazoazide and phenylpentazole in the proportion of $Q_{c,r} = 2.03 \pm 0.05$, and benzenediazoazide decomposes at a rate of $k_{c,d,I} = 5.7 \times 10^{-3} \text{ sec}^{-1}$. The same reaction, carried out in the presence of a second phase (phase II: carbon tetrachloride + *n*-hexane, 22 + 78 wt.-%; approximately of the same density as phase I, favoring intimate contact of the liquid phases), with rapid stirring, though it reveals no measurable change in the ratio of benzenediazoazide to phenylpentazole ($Q_{c,r,I+II} = 1.96 \pm 0.05$), shows a considerably slower rate of benzenediazoazide decomposition ($k_{c,d,I+II} = 2.3 \times 10^{-3} \text{ sec}^{-1}$). From the fact that in the two-phase system the decomposition of benzenediazoazide is slower than in phase I alone, one can conclude the following: In the two-phase system the benzenediazoazide formed in phase I migrates, in a significant amount, to phase II, where its decomposition ensues.

TABLE IV
THE INFLUENCE OF THE SOLVENT UPON THE
RATIO $Q_{c,r}$ AT -30° ^a

Solvent, wt. - %	$Q_{c,r}$
Methanol/water (50 + 50)	1.84
Methanol/water (75 + 25)	2.00
Methanol	2.45
Methanol/tetrahydrofuran (50 + 50)	2.77
Methanol/ <i>n</i> -butanol (50 + 50)	2.92
Methanol/ <i>n</i> -butanol (10 + 90)	3.16

^a I. Ugi, Habilitation Thesis, University of Munich, 1959.

A relevant difference between the two mechanisms under discussion is that, whereas in the mechanism of Section III, A, 1 [cf. Eq. (3)] the observed ratio ($Q_{c,r} = k_{c,i}/k_{r,i}$) is independent of $k_{c,d}$, in the alternative reaction mechanism [see Eq. (5)] $Q_{c,r}$ is a function of $k_{c,d}$ ($Q_{c,r} \approx k_{c,d}/k_{c,i}$, if $k_{r,i} \ll k_{c,d}$, $k_{c,i}$). As has been shown above $Q_{c,r,I} \approx Q_{c,r,I+II}$ and $k_{c,d,I} > k_{c,d,I+II}$, which indicates that $Q_{c,r}$ is independent of $k_{c,d}$. In combination with the fact that in one-phase systems the value of $Q_{c,r}$ depends upon the solvent (see Table IV), the results of the "two-

phase experiment" suggest an independent formation and decomposition of benzenediazoazide and phenylpentazole as discussed in Section III, A, 1. However, it could be objected that benzenediazoazide could exist in two isomeric forms (e.g. *cis* and *trans* forms), one of which would very rapidly be transformed into phenylpentazole while the other isomer would decompose independently, and that the ratio in which these isomeric forms of benzenediazoazide are generated corresponds to the observed ratio $Q_{c,r}$. Yet such different chemical behavior of the stereoisomers of benzenediazoazide has been shown to be improbable by Roberts,²⁴ who calculated the "flexibility" of the benzenediazoazide molecule.

The influence of the solvent on the decomposition rate of phenylpentazole (see Table II) supports the one-step four-centered 1,3-fission of phenylpentazole according to **22**. The correlation of the polarity of the transition states of 1,3-additions, which resemble the assumed transition state of the phenylpentazole decomposition (**22**), and solvent effects has recently been discussed by Huisgen.²⁶

4. The Irreversibility of the Decomposition of Arylpentazoles

In view of the enthalpy and activation energy (see Section II, B, 1) of the decomposition of arylpentazoles the activation energy for the reversal of the decomposition, the 1,3-addition of elementary nitrogen to arylazides, can be estimated to be 25–30 kcal/mole, an amount which does not exclude the reaction. To ascertain whether the decomposition of arylpentazoles is a reversible reaction, *p*-ethoxyphenylazide- $[\beta\text{-N}^{15}]$ (see Section II, B, 3) adsorbed on charcoal was exposed to unlabeled nitrogen (45–50°, 380 atm, 100 hr), but the anticipated exchange of N^{15} between the reactants was not detected.^{12, 13, 17}

B. THE REACTIONS OF AZIDE AND SUBSTITUTED BENZENEDIAZONIUM IONS

It seems reasonable to assume that in regard to their formation and decomposition the derivatives of phenylpentazole correspond roughly to the unsubstituted compound (see Table V). The rate data for *m*- and *p*-substituted phenylpentazoles conform to the Hammett equation²⁷ with $\rho = +1.01$. Finally, the high rate of decomposition and

²⁶ R. Huisgen, *Proc. Chem. Soc.* 357 (1961); *Naturw. Rundschau* **14**, 43 (1961); *Angew. Chem.* **75**, 742 (1963).

²⁷ L. P. Hammett, "Physical Organic Chemistry." McGraw-Hill, New York, 1940. H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).

low formation tendency of *o*-substituted phenylpentazoles are worth mentioning.

TABLE V
THE FORMATION AND DECOMPOSITION OF SUBSTITUTED
PHENYLPENTAZOLES IN METHANOL AT 0°^a

Substituted phenylpentazole	$Q_{c,r}$	$k_{r,d} \times 10^4 \text{ (sec}^{-1}\text{)}$
<i>p</i> -NO ₂ -	6.1 (10.1) ^b	59
<i>p</i> -(CH ₃) ₂ NH ⁺	—	51
<i>m</i> -NO ₂ -	4.6 (4.0)	36
<i>m</i> -Cl-	3.3 (5.7)	23
<i>p</i> -Cl-	3.5	12.1
H-	3.2	8.4
<i>m</i> -CH ₃ -	2.6	7.6
<i>m</i> -HO-	2.0	7.1
<i>p</i> -CH ₃ -	1.9 (1.6)	5.6
<i>p</i> -HO-	1.9	3.2
<i>p</i> -C ₂ H ₅ O-	1.9 (0.9)	3.0
<i>p</i> -(CH ₃) ₂ N-	1.2	1.7
<i>p</i> -O ⁻ -	—	0.9
<i>o</i> -NO ₂ -	24	92
<i>o</i> -Cl-	8	86
<i>o</i> -CH ₃ -	3.4	31
<i>o,o,p</i> -(CH ₃) ₃ -	13	23

^a I. Ugi and R. Huisgen, *Chem. Ber.* **91**, 531 (1958).

^b K. Clusius and M. Vecchi [*Helv. Chim. Acta.* **39**, 1469 (1956)] observed the values shown in brackets when azide and diazonium- $[\beta\text{-N}^{15}]$ ions were allowed to react in water at 0°.

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